ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

Publication Office: Prince and Lemon Sts., Lancaster, Pa.
Executive Office: 4200 Pine Street, Philadelphia, Pa.

VOL. 30 (O.S., Vol. XXXIV) FEBRUARY, 1949 NUMBER 2

CONTENTS

Page

Diagnostic Significance of Urinary Hormonal Assays: Report of Experience with Measurements of 17-Ketosteroids and Follicle Stimulating Hormone in the Urine. Roberto F. Escamilla 249
The Hemodynamic Effects of Sympathectomy in Essential Hypertension. Robert W. Wilkins, James W. Culbertson and Meyer H. Halperin 291
Results of High Dorsolumbar Sympathectomy for Hypertension. James A. Evans and Carl C. Barthels 307
Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions. I. Visualization of Aneurysms and Peripheral Arteries. Norman E. Freeman and Earl R. Miller 330
The Treatment of Acute Putrid Lung Abscess with Penicillin and Sulfadiazine. Barnet P. Stivelman and Julius Kaver 343
Clinical Evidence of Sensitivity to Gonadotropins in Allergic Women. E. W. Phillips 364
Observations on Relapses in Pernicious Anemia. Edgar Jones, Clifford C. Tillman and William J. Darby 374
The Use of a Nitrogen Mustard in Hodgkin's Disease and Lymphosarcoma. Andrew H. Meyer and W. C. Overmiller 381
The Use of the Exercise Test in the Diagnosis of Coronary Insufficiency. Milton Grossman, William W. Weinstein and Louis N. Katz 387
The Effect of Caronamide on the Blood Concentration of Penicillin Following Oral and Intramuscular Administration of Penicillin. William W. Zeller, Mark H. Lepper, Jay A. Robinson, Harold L. Hirsh and Harry F. Dowling 398
Case Reports:
Hemolytic Anemia Associated with Atypical Hemagglutinins. William J. Kuhns and Philip F. Wagley 408
Observations on the Fate of the Accessory Conductor in Wolff-Parkinson-White Syndrome; Report of a Case Demonstrating Return to Normal Conduction Following Acute Illness. David Littmann 423
Vitamin D Intoxication Due to Ertron: Report of Two Cases. Charles K. Donegan, Addison L. Messer and Edward S. Orgain 429
Editorial—Anticoagulants in the Treatment of Coronary Thrombosis 436
Reviews 440
College News Notes 444
Program, 30th Annual Session of the American College of Physicians, New York City, March 28 to April 1, 1949. 453
Abridged Minutes, Board of Regents Meeting 476

Subscription per volume or per annum, net postpaid, $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of March 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 1925, embodied in paragraph 4, section 538, P. L. & R., authorized October 7, 1936.

THIRTIETH ANNUAL SESSION—NEW YORK CITY—MARCH 28–APRIL 1, 1949

CONVENTION NUMBER

3rd EDITION PUBLISHED 1948

ILLUSTRATIVE ELECTROCARDIOGRAPHY

By

Julius Burstein, A.B., M.D., Visiting Electrocardiographer and Chief of the Cardiac Clinic, Morrisania City Hospital, N.Y.C.; Assoc. Cardiologist and Chief of the Cardiac Clinic, Jewish Memorial Hospital, N.Y.C., and

Nathan Bloom, M.D., F.A.C.P., Associate Professor of Medicine and Chief of the Department of Electrocardiography, Medical College of Virginia, Richmond.

The subject matter in this atlas is arranged in a definite and practical sequence presenting first the fundamental principles of electrocardiography followed by a series of tracings displaying the normal electrocardiogram with variations within the normal range and then by the major portion of the book which takes up fully the abnormal electrocardiograms. These records present progressive changes in the pathological physiology of the heart and each record emphasizes a single type of abnormality. The chapter on Radiology of The Heart is contributed by Dr. Philip Slater, Director of Radiology, Seaview and Jewish Memorial Hospitals, N.Y.C.

As Reviewed in The Military Surgeon in Oct. 1948

The entire field of electrocardiographic abnormalities is presented in this atlas type of reference work. It consists of a series of electrocardiographic tracings demonstrating each type of physiologic and pathologic abnormality with brief explanations opposite each plate. Precordial leads and the "Phonocardiogram" receive proper consideration in addition to a fine chapter on "Radiology of the Heart." This is a brief, up-to-date graphic presentation of electrocardiography.

As Reviewed in The N.Y. State Journal of Medicine on Dec. 1, 1948

This third edition is an up-to-date and valuable book of references for the practitioner interested in electrocardiography. The tracings are clear and plainly marked, and the interpretation can be followed easily. The chapters on right and left ventricular strain are excellent. The subject of multiple precordial leads is presented in detail. The chapters on pericarditis, splanchnicectomy, and multiple myocardial lesions are very interesting and instructive. It is a useful addition to the literature of cardiology.

325 pages. 559 Tracings and Illustrations, 3rd (1948) Edition. $6.00

Order Through Bookstores or

APPLETON-CENTURY-CROFTS, INC., 35 E. 32nd St., N.Y. 1, N.Y.

Forthcoming Publications

SYPHILIS: Its Course and Management

Since the discovery of penicillin and the application of its use to the treatment of syphilis, there have been revolutionary changes in the techniques and methods of treatment. The radical alteration of therapeutic application makes it necessary for the entire medical and public health professions to be reoriented in their thinking as well as in their methods of treatment.

The busy practitioner will welcome Dr. Thomas' presentation of the new methods of diagnosis, prognosis, and treatment. It shows the average doctor that he can treat syphilis cases very effectively himself, that he does not need to send them for prolonged treatment to a clinic or specialist.

by Evan Thomas, M.D., Professor of Clinical Medicine, New York University College of Medicine; Director, Rapid Treatment Center and Visiting Physician, Bellevue Hospital, New York; Consultant, United States Public Health Service.

330 pages
Probably $5.00

THE VENEREAL DISEASES

The importance of venereal diseases and the rapid progress in research on them, together with changes in treatment, call for a general review of the diagnosis and treatment of venereal diseases. This has been done to a remarkably fine degree in this new edition. Excellent illustrations along with a masterful text presentation make this a most practical book for the practitioner or student.

Treatment is given its proper consideration after each discussion of the various facets of the diseases. The older, sound and proven methods are reviewed thoroughly, but the important change in this edition is the inclusion of treatment methods using penicillin. Techniques, precautions, laboratory methods, taking of specimens, injections, etc. are discussed in a section titled "Practical Instructions."

by James Marshall, M.D., Director, Venereal Diseases Clinic, Royal Northern Hospital, London; Consulting Dermatologist, Central Middlesex County Hospital; lately Adviser in Venereology to the War Office.

369 pages **$5.50**

The Macmillan Company

60 Fifth Avenue
New York 11, N. Y.

Books of Interest to Practicing Physicians

Be Sure to Visit the Lea & Febiger Exhibit at Booth 55
New York Session of the American College of Physicians, March 28 to April 1, 1949

JOSLIN—TREATMENT of DIABETES MELLITUS
By ELLIOTT P. JOSLIN, M.D., Professor Emeritus, Harvard Medical School; and Associates.
Eighth Edition. 861 pages, illustrated, 1 plate in color. $10.00

JOSLIN—DIABETIC MANUAL For Doctor and Patient
By ELLIOTT P. JOSLIN, M.D.
New (8th) Edition. 260 pages, illustrated, 1 plate in color. $2.50

LICHTMAN—DISEASES OF LIVER, GALLBLADDER & BILE DUCTS
By S. S. LICHTMAN, M.D., F.A.C.P., Mount Sinai Hospital; Columbia University and Cornell University Medical College.
New (2nd) Edition. In press.

GRAY—ANATOMY
By HENRY GRAY, F.R.S. Edited by CHARLES MAYO GOSS, M.D., Louisiana State University, New Orleans.
New (25th) Edition. 1478 pages, 1263 illustrations, mostly in color. $14.00

KRAINES—THERAPY of the NEUROSES and PSYCHOSES
By SAMUEL HENRY KRAINES, M.D., University of Illinois, College of Medicine, Chicago.
New (3rd) Edition. 642 pages. $6.50

MUSSER—INTERNAL MEDICINE
Edited by the late JOHN H. MUSSER, M.D., Tulane University of Louisiana School of Medicine.
Fourth Edition. 1518 pages, illustrated. $10.00

LEVINSON and MacFATE—CLINICAL LABORATORY DIAGNOSIS
By SAMUEL A. LEVINSON, M.D., and ROBERT P. MacFATE, CH.E., M.D., University of Illinois, College of Medicine, Chicago.
Third Edition. 971 pages, 192 illustrations and 15 plates, 7 in color. $10.00

BURCH and REASER—PRIMER of CARDIOLOGY
By GEORGE E. BURCH, M.D., and PAUL REASER, M.D., Tulane University School of Medicine, New Orleans.
272 pages, 203 illustrations. $4.50

SOFFER—DISEASES of the ADRENALS
By LOUIS J. SOFFER, M.D., Columbia University, New York.
New (2nd) Edition. 320 pages, 45 illustrations, 3 plates in color. $6.50

PORTIS—DISEASES of the DIGESTIVE SYSTEM
Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P., University of Illinois Medical School, Chicago.
Second Edition. 932 pages, 182 illustrations. $11.00

THIENES and HALEY—CLINICAL TOXICOLOGY
By CLINTON H. THIENES, M.D., and THOMAS J. HALEY, PH.D., University of Southern California, Los Angeles.
New (2nd) Edition. 373 pages, illustrated. $4.75

ORMSBY and MONTGOMERY—DISEASES of the SKIN
By OLIVER S. ORMSBY, M.D., University of Illinois; and HAMILTON MONTGOMERY, M.D., University of Minnesota.
New (7th) Edition. 1462 pages, 764 illustrations on 683 figures, 18 in color on 11 plates. $18.00

WINTROBE—CLINICAL HEMATOLOGY
By MAXWELL M. WINTROBE, M.D., University of Utah, School of Medicine, Salt Lake City.
Second Edition. 862 pages, 197 illustrations, 14 plates, 10 in color. $11.00

HADEN—PRINCIPLES of HEMATOLOGY
By RUSSELL L. HADEN, M.D., Cleveland Clinic.
Third Edition. 366 pages, 171 illustrations, including 173 original photomicrographs and 95 original charts and drawings. $5.00

KOVÁCS—ELECTROTHERAPY and LIGHT THERAPY
By RICHARD KOVÁCS, M.D., New York Polyclinic Medical School and Hospital.
Fifth Edition. 694 pages, 352 illustrations, 1 plate in color. $8.50

KOVÁCS—MANUAL of PHYSICAL THERAPY
By RICHARD KOVÁCS, M.D.
Third Edition. 309 pages, 118 illustrations. $3.25

LEA & FEBIGER
Washington Square
Philadelphia 6, Pa.

Please send books indicated. ☐ Check enclosed. ☐ Bill me. ☐ Charge on your partial payment plan.

DR. (please print) ..... ADDRESS .....

CITY ..... ZONE ..... STATE .....

(A.I.M. 2-49)

LIPPINCOTT SELECTED PROFESSIONAL BOOKS

New approaches to the science of diagnosis

Signs and Symptoms: Their Clinical Interpretation

Edited by CYRIL M. MACBRYDE, M.D., F.A.C.P., With 20 Contributing Authors

439 Pages.
74 Illustrations,
7 Color Plates.
$12.00

This standard text and reference on applied clinical pathological physiology and basic diagnostic processes is unique in its approach to understanding the manifestations of disease. It starts with the symptom and proceeds logically, as the practitioner must, toward the diagnosis. *"Here in concentrated form is graduate education of high quality. The illustrations are excellent and adequately supplement the text . . ."*—JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

Diagnosis in Daily Practice:

An Office Routine Based on the Incidence of Disease

By BENJAMIN V. WHITE, M.D. and CHARLES F. GESCHICKTER, M.D.

693 Pages.
360 Illustrations.
$15.00

Three essential steps in diagnosis are concisely presented in this book: how to elicit important signs, simplify the procedure of differential diagnosis and evaluate clinical findings through the use of pertinent data. A complete integration of the knowledge acquired in hospital training in diagnosis and its application to general practice. *"The authors are to be congratulated for . . . the practical selectivity with which they have combined the ideas and ideals of the pathologist and the clinician into such a splendid volume."*—THE CONNECTICUT STATE MEDICAL JOURNAL.

Lippincott Books Philadelphia London Montreal

J. B. LIPPINCOTT COMPANY, East Washington Square, Philadelphia 5, Pa.
Enter my order and send me: ☐ *MacBryde*, Signs & Symptoms, $12.00
☐ *White & Geschickter*, Diagnosis in Daily Practice, $15.00

Name ..... ☐ Cash enclosed
Address ..... ☐ Send C.O.D.
City, Zone, State ..... ☐ Charge my account

At Booths 80 *and* 81,

OXFORD UNIVERSITY PRESS cordially invites you to visit its representatives and to examine at your pleasure the entire list of *Oxford Medical Publications*, including, among other current and recent new books and new editions:

The new OXFORD LOOSE-LEAF MEDICINE

Now comprising 294 separate, complete medical monographs written by international authorities; newly printed on nearly 14,000 pages encased in 14 newly-designed, loose-leaf volumes and available this spring for the first time in three years. $150.00

Allen: **SEXUAL PERVERSIONS AND ABNORMALITIES (2nd Edition)**

Barach: **DIABETES AND ITS TREATMENT**

Barach: **FOODS AND FACTS FOR THE DIABETIC**

Boyce: **ACUTE APPENDICITIS AND ITS COMPLICATIONS**

Brodal: **NEUROLOGICAL ANATOMY IN RELATION TO CLINICAL MEDICINE**

Davidson: **PRACTICAL MANUAL OF DISEASES OF THE CHEST (3rd Edition)**

Fulton: **FUNCTIONAL LOCALISATION IN THE FRONTAL LOBES AND CEREBELLUM**

Fulton: **PHYSIOLOGY OF THE NERVOUS SYSTEM (3rd Edition)**

Hill: **OPERATIVE SURGERY**

Kayne, Pagel and O'Shaughnessy: **PULMONARY TUBERCULOSIS (2nd Edition)**

Meleney: **TREATISE ON SURGICAL INFECTIONS**

Simpson: **MAJOR ENDOCRINE DISORDERS (2nd Edition)**

Truex and Kellner: **DETAILED ATLAS OF THE HEAD AND NECK**

Wolff: **HEADACHE AND OTHER HEAD PAIN**

OXFORD UNIVERSITY PRESS, INC.

114 Fifth Avenue, New York 11, N.Y.

DISTINGUISHED HOEBER BOOKS

At Booth 75 all HOEBER books will be on display. A few important new titles are listed below.

ALVAREZ'

Introduction to Gastroenterology

New 4th Edition of a classic work. 925 pp., 269 illus. $12.50

FOWLER'S

Clinical Hematology

New 2nd edition of the internist's guide to blood disorders.
550 pp., 110 illus., 8 color plates. $8.50

EVANS'

Cardiology

A concise, authoritative summary of today's clinical practice.
341 pp., 304 illus., $7.50

HARRIS'

Modern Trends in Psychological Medicine

By 19 international authorities. 465 pp., 25 illus. $10.00

●

PAUL B. HOEBER, INC.
Medical Book Department of Harper & Brothers
49 East 33rd Street, New York 16, N.Y.

Please send me, ON APPROVAL

☐ Alvarez' Gastroenterology $12.50
☐ Fowler's Clinical Hematology ..... $ 8.50
☐ Evans' Cardiology ..... $ 7.50
☐ Harris' Psychological Medicine $10.00

☐ Charge my account ☐ Check Enclosed

Name .....

Street ..... City ..... Zone .... State .....

NEW BOOKS FOR THE INTERNIST

ALBRIGHT and REIFENSTEIN—Parathyroid Glands and Metabolic Bone Disease

These selected studies were chosen because the authors had had first hand experience with the subjects under consideration and felt they had something to contribute to the general knowledge. In effect, the studies comprise a summary of the work carried out on the Metabolic Ward of the Massachusetts General Hospital over a period of twenty-four years under a series of researchers.

410 pp., 157 figs., $8.00

REHFUSS, ALBRECHT, and PRICE—Practical Therapeutics

This new and most unusual textbook of therapeutics presents symptomatic and specific therapy, with literally hundreds of prescriptions and detailed instructions on how to handle the situations a physician encounters in his everyday practice. The text gives all phases of treatment in an easy to read, easy to consult outline form. The full page plates, closely allied to the text, show at a glance symptoms, etiology, diagnosis, differential diagnosis, and complications.

840 pp., 7 figs., 70 plates, $15.00

KRANTZ and CARR—Pharmacologic Principles of Medical Practice

The key to the approach of this new text is embodied in the title: "Principles" explain what to do and why, and "Practice," how to do it and when. With this in mind the authors have emphasized the clinical application of drugs, since the text is intended as a guide for the medical student and for the practicing physician who daily uses drugs in the treatment of his patients.

1000 pp., 94 figs., 24 portraits, $10.00

MEAKINS—Symptoms in Diagnosis, 2nd edition

Here is a concise presentation of the commonest—and often the most illusive—symptoms. Good clinical sense is evident on every page of the text and in the careful selection of the illustrations. In this new edition, the entire text has been revised, largely rewritten, and greatly expanded. Four of the chapters were written by younger colleagues of Dr. Meakins thereby giving a fresh slant to the problems under consideration.

350 pp., 112 figs., $7.50

FRIED—Bronchiogenic Carcinoma and Adenoma

Dr. Fried's book is based on extensive studies of large clinical and post mortem material. It covers both pathological and clinical aspects of all types of bronchiogenic and mediastinal tumors. Throughout, great emphasis is placed on the vital importance of early diagnosis. To this end, all the modern diagnostic methods at the disposal of the physician are discussed, as well as etiology and treatment.

326 pp., 118 figs., $6.00

GRULEE—The Child in Health and Disease

Seventy-five contributors from all sections of the United States present an overall picture of the modern practice of pediatrics. All are outstanding in their fields. The volume stresses the practical side of pediatrics, as a reminder that the true value of investigation is dependent on bedside application. It would be difficult to mention an aspect of pediatric practice that is not covered in detail sufficient for treating the young patient intelligently and according to modern methods.

1079 pp., 224 figs., 3 plates, $12.00

See copies of these books in our Exhibit, Booth No. 8, at the Convention in New York City, March 28–April 1

THE WILLIAMS & WILKINS COMPANY

Mt. Royal and Guilford Aves. **Baltimore 2, Maryland**

Please Mention this Journal when writing to Advertisers

A Monumental New Book

GEORGE R. MINOT SYMPOSIUM OF HEMATOLOGY

William Dameshek, M.D., and F. H. Laskey Taylor, M.D., Editors, Boston, Massachusetts.

Some 140 leading clinicians and outstanding researchers have contributed to make this book a veritable treasury of present-day knowledge of hematology. The 84 contributions are grouped in the following sections: Pernicious Anemia, Hemolytic Anemia, Other Forms of Anemia, Blood Clotting Phenomena and Hemorrhagic Disease, Leukemia, Biologic and Cytologic Reactions, Biochemical Aspects.

Dedicated to the dean of American hematology, the symposium appeared originally in several of the issues of BLOOD, The Journal of Hematology. In the new volume the material, rearranged systematically, is made available in permanent form. The book has 975 pages, 268 illustrations, 206 tables, bibliographies and complete index.

Regular edition, bound in red buckram, gold stamped ***$12.00***
Deluxe edition, bound in red leather, gold stamped ***$25.00***

Two Recent Monographs

SHOCK and Allied Forms of Failure of the Circulation

By H. A. Davis, M.D., College of Medical Evangelists, Los Angeles Division.

This is the first book to consolidate and evaluate the results of research and clinical experience and to outline practical approaches for diagnosis and treatment for every type of shock.

600 pages *55 illustrations* ***$12.00***

VENOUS THROMBOSIS AND PULMONARY EMBOLISM

By Harold Neuhof, M.D., Columbia University.

"No physician or surgeon can read this monograph without gaining a respect for the danger of venous thrombosis in both surgery and medicine, nor will he avoid using prophylactic measures." AMERICAN JOURNAL OF MEDICAL SCIENCES.

159 pages *31 illustrations* ***$4.50***

And a Timely Survey

PROGRESS IN CLINICAL MEDICINE

Edited by Raymond Daley, M.D., London, and Henry G. Miller, M.D., Newcastle-on-Tyne.

"A brief refresher course . . . an excellent review of important recent advances in the field of clinical medicine." JOURNAL OF THE A.M.A.

360 pages *39 illustrations* ***$6.00***

Won't you see us at the Meeting of the A.C.P., Space 34?

Published by

GRUNE & STRATTON, INC.

381 Fourth Ave., New York 16, N. Y.

ORDER FORM

Please send, on approval, a copy of:

MINOT SYMPOSIUM
☐ *Regular Edition,* $12.00
☐ *Deluxe Edition* $25.00

☐ SHOCK $12.00
☐ VENOUS THROMBOSIS $4.50
☐ PROGRESS IN CLINICAL MEDICINE $6.00

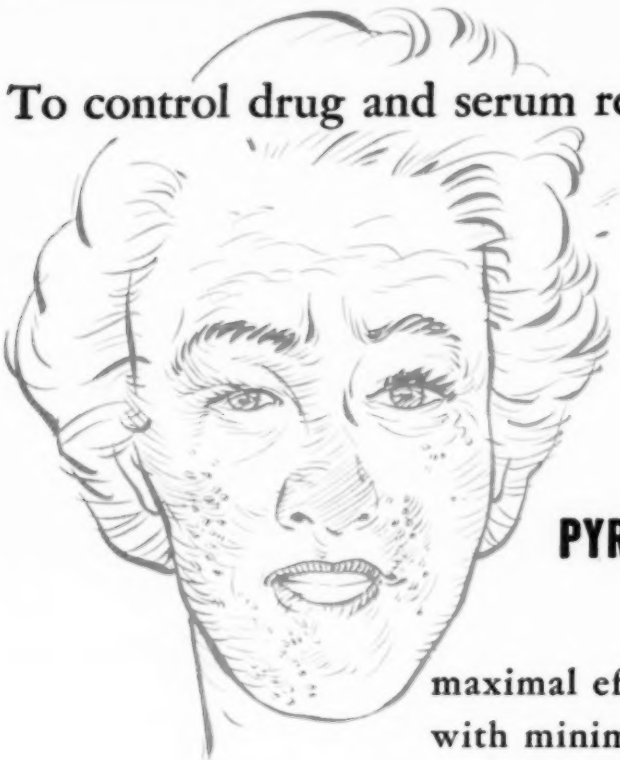
Name.....

Address.....

☐ *Charge my account* ☐ *Check enclosed*

Please Mention this Journal when writing to Advertisers

To control drug and serum reactions...



PYRIBENZAMINE

maximal effectiveness with minimal side effects

"The itching is benefited most, although the edema is usually also reduced and held in abeyance."

In numerous clinical studies, the efficacy of Pyribenzamine hydrochloride has been demonstrated in prophylaxis and treatment of allergic reaction to liver extract, penicillin, the sulfonamides and certain other drugs.[1,2,3] The administration of Pyribenzamine prior to a desensitizing dose of allergen is frequently successful in preventing constitutional reactions.[4]

The average dose for adults is 50 mg. 3 to 4 times daily, which in some cases may be reduced, or in the absence of side effects may be increased up to 600 mg. per day. Pyribenzamine is distinguished by high potency with minimal side effects.

1. Feinberg, S. M.: Postgrad. Med., 3: 92, Feb., 1948; 2. Arbesman, C. E., et al.: J. Allergy, 17: 275, Sept., 1946; 3. Feinberg, S. M., and Friedlaender, S.: Am. J. Med. Sci., 213: 58, Jan., 1947; 4. Fuchs, A. M., et al.: J. Allergy, 18: 385, Nov., 1947.

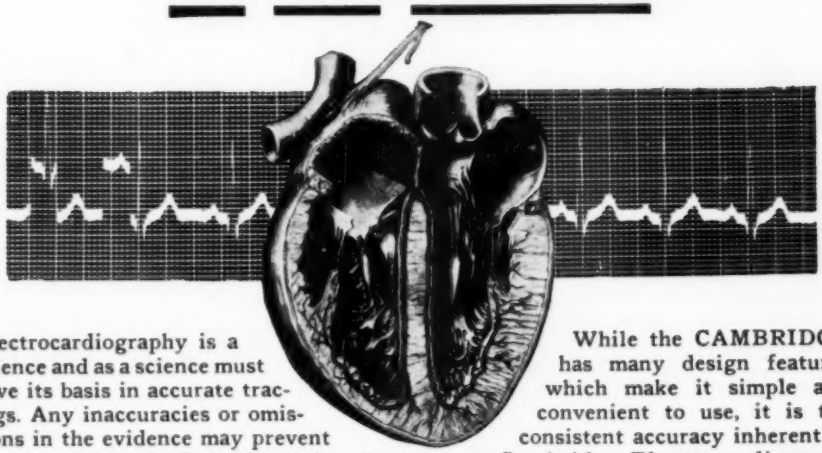
PYRIBENZAMINE: Scored tablets 50 mg., bottles of 50, 500 and 1000; Elixir 5 mg. per cc. bottles of 1 pint and 1 gallon. (Council Accepted.)

Ciba PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

PYRIBENZAMINE (brand of tripelennamine)—Trade Mark Reg. U.S. Pat. Off. 2/1412M

In Electrocardiography— Diagnosis is only as accurate

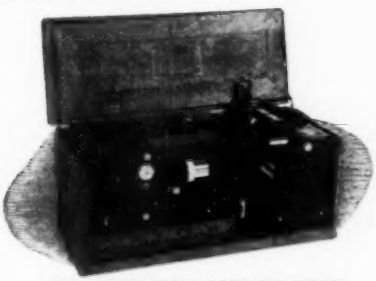
as the Record



Electrocardiography is a science and as a science must have its basis in accurate tracings. Any inaccuracies or omissions in the evidence may prevent accurate diagnosis. It is imperative that the Electrocardiograms be of unquestioned accuracy.

While the CAMBRIDGE has many design features which make it simple and convenient to use, it is the consistent accuracy inherent in every Cambridge Electrocardiograph that has made this instrument the choice of discriminating Cardiologists . . . everywhere.

When you select a CAMBRIDGE, Doctor, you buy the assurance of accurate records for your lifetime in practice. You can afford no less, nor can you buy more.



THE "SIMPLI-TROL" PORTABLE MODEL

. . . for use in private practice, is contained in one case, 8" x 10" x 19", and weighs only 30 lbs. Mobile and Research Models for Hospital use are also available. Line operation from any electric outlet eliminates battery nuisance. All models may be arranged to record heart sounds, pulse, and electrocardiogram simultaneously.

Send for descriptive literature

CAMBRIDGE INSTRUMENT CO., INC.
3715 Grand Central Terminal
New York 17

Chicago 12, 2400 W. Madison St.
Philadelphia 4, 135 S. 36th St.
Cleveland 15, 1720 Euclid Ave.

Pioneer Manufacturers of the Electrocardiograph

CAMBRIDGE ALSO MAKES ELECTROKYMOGRAPHS, PLETHSYMOGRAPHS, AMPLIFYING STETHOSCOPES, RESEARCH pH METERS, BLOOD PRESSURE RECORDERS, INSTRUMENTS FOR MEASURING RADIOACTIVITY, ETC.

CAMBRIDGE
all-electric
ELECTROCARDIOGRAPH

FEVER—
WHAT TO DO FOR IT

There is no better way of satisfying the thirst of the febrile subject than by letting him drink

Kalak (R)

(An artificially produced carbonated alkaline water)

It is an invitingly pleasant drink to the parched. It supplies both fluid and minerals, thus aiding in the prevention of acidosis either from disease or drugs (the salicylates, the sulphas and the extracts from molds).

Available at all pharmacies

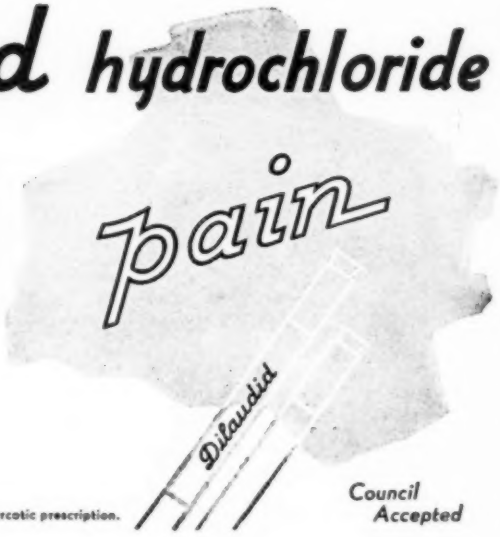
KALAK WATER CO. OF NEW YORK, INC.
30 ROCKEFELLER PLAZA NEW YORK 20, N.Y.

Dilaudid hydrochloride

For pain in acute or hopelessly chronic conditions when an opiate is required, try Dilaudid hydrochloride for quick relief.

DOSE: 1/48 to 1/20 grain.

In hypodermic and oral tablets, rectal suppositories and powder.



Council Accepted

• Dilaudid HCl, dihydromorphinone HCl, requires a narcotic prescription.

BILHUBER-KNOLL CORP. ORANGE, NEW JERSEY

Crystalline Sodium Penicillin G

"Crystalline preparations designated as Crystalline Penicillin G are required to contain 90 per cent of G . . . the sodium salt to have a potency of not less than 1500 units per milligram"—*New and Nonofficial Remedies. American Medical Association, Chicago, Illinois, 1947. p. 145.*

Bristol Crystalline Sodium Penicillin G is available in 20 cc. vials containing 100,000, 200,000, or 500,000 units. Refrigeration in storage is not required. Sterile solutions are readily prepared by a simple injection of the diluent—normal saline solution, pyrogen-free distilled water, or 5 per cent dextrose solution—through the rubber cap of the vial. Solutions, once prepared, should be kept refrigerated and used within three days.

Bristol
LABORATORIES INC
SYRACUSE, NEW YORK

wes·sal
TRADE MARK

the only salt substitute that tastes exactly like salt

wes·sal is a joy to patients on low-salt (sodium) diets. It's the *only* salt substitute that makes food taste *exactly* as if seasoned with salt. No bitter, no disagreeable taste. Used freely at the table—in cooking and baking. ● Sodium-free, safe, convenient, ***wes·sal*** assures eating without cheating, a minimum intake of harmful sodium, better nourishment, and grateful, happier, patients in . . .

congestive heart failure • hypertension • toxemias of pregnancy

send for tasting samples

WESTWOOD PHARMACEUTICALS, Dept. AI ● 468 Dewitt St., Buffalo 13, N. Y.
division of Foster-Milburn Co.

wes·sal is a solution of lithium chloride with small amounts of citric acid and potassium iodide (iodizing traces). Bottles of 2¼ oz.

Effective in combating simple depression

When the cause of the underlying emotional disturbance is apparent—and when it has been properly ventilated—'Benzedrine' Sulfate has proved its effectiveness in the treatment of mild but persistent psychogenic depressions, such as may be found:

Attending ***old age***
With prolonged ***postoperative recovery***
Accompanying ***prolonged pain***
When psychopathic problems develop ***after childbirth***
Precipitated by ***the menopause***
With debilitating or crippling ***chronic organic disease***

Benzedrine® Sulfate tablets • elixir

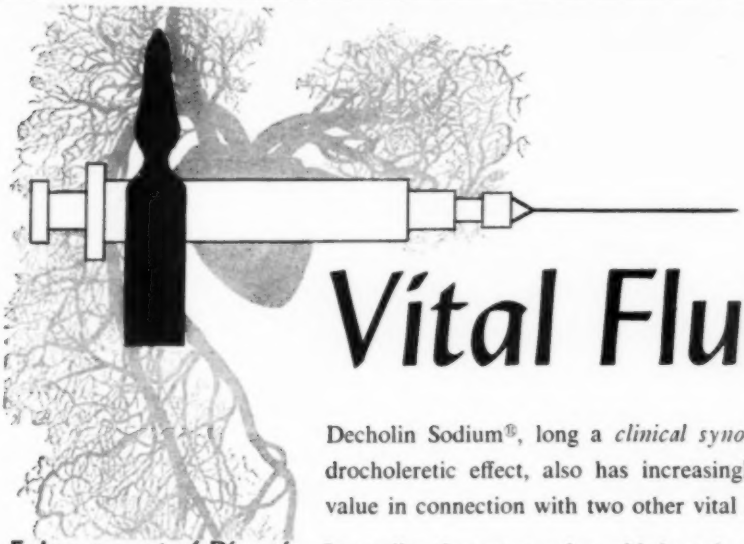
(racemic amphetamine sulfate, S.K.F.)

one of the fundamental drugs in medicine

Smith, Kline & French Laboratories, Philadelphia

®T. M. Reg. U. S. Pat. Off.

272



Vital Fluids

Decholin Sodium®, long a *clinical synonym* for hydrocholeretic effect, also has increasingly-recognized value in connection with two other vital fluids.

Enhancement of Diuresis. In cardiac decompensation with hepatic engorgement, Decholin Sodium given alone produces mild diuresis. More often it is administered simultaneously with mercurial diuretics to potentiate their action and reduce their dose.

Blood Circulation Time. Arm-to-tongue blood circulation time is reliably and relatively safely determined by injection of Decholin Sodium into a cubital vein. If desired, an arm-to-lung time test is readily included in the procedure by adding ether to the Decholin Sodium injection.

Decholin Sodium®

sodium dehydrocholate

supplied in 20% aqueous solution for intravenous administration. Available now in ampuls of 3 cc., 5 cc. and 10 cc.; boxes of 3 and 20 ampuls.

The booklets, "Decholin Sodium in Blood Velocity Determination" and "The Diuretic Action of Decholin Sodium" are now available—and will be sent upon your request.

AMES

AMES COMPANY, INC.

ELKHART, INDIANA

ERA

THE RECORD AUTOMATIC ELECTROCARDIOGRAPH

Another step forward has been made in the Field of Electrocardiography. With the BECK-LEE Record Automatic camera a true electrocardiogram emerges from the instrument a few seconds after the patient has been tested. The record is permanent and can be evaluated immediately.

Here is the ultimate in convenience plus the accuracy of the Einthoven quartz string galvanometer and true photo-electric timing.

Priority deliveries of the BECK-LEE Model RA camera are now being made.

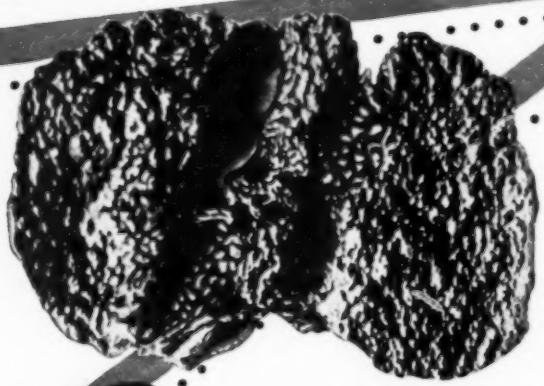
THE BECK-LEE ELECTROCARDIOGRAPHS

Model E, $645 ★ Model ERA, $725

BECK-LEE CORPORATION

630 West Jackson Boulevard • Chicago 6, U.S.A.

To forestall this eventuality



C.S.C. Syrup **CHOLINE BICARBONATE**

WHEN instituted early and in conjunction with a diet providing large amounts of protein and B complex vitamins, Choline therapy interrupts the chain of events in the development of portal cirrhosis. Thus fatty infiltration of the liver, the forerunner of cirrhosis, is overcome, and the fatal complicating cirrhosis is either forestalled or prevented.

Syrup Choline Bicarbonate-C.S.C., an entirely new choline preparation for therapeutic use, is an advantageous means of administering choline. It is an unusually palatable mixture, provides the equivalent of 12.5 per cent choline base or 14.4 per cent choline chloride, and may be given in full therapeutic dosage without gastric intolerance or nausea.

Available at all pharmacies in one pint bottles.

C.S.C. Pharmaceuticals

A DIVISION OF COMMERCIAL SOLVENTS CORPORATION • 17 EAST 42nd STREET • NEW YORK 17, N. Y.

Please Mention this Journal when writing to Advertisers

During the *"springing-up"* period... give them

. . . the natural vitamins A and D—in tablets so remarkably pleasant tasting that children delight in chewing them.

. . . a well tolerated form—no excess calories, appetite is not affected.

. . . full potency—each tablet is equivalent, in vitamin content, to one teaspoonful of cod liver oil* and supplies 312 units of vitamin D, wholly derived from cod liver oil, and 3,120 units of vitamin A supplied by cod liver oil concentrate adjusted and standardized with fish liver oils.

. . . an economical preparation—especially suited to maintaining antirachitic protection through the growth years. Also available in "drop-dosage" Liquid for infants and in higher potency capsules.

White Laboratories, Inc., Pharmaceutical Manufacturers, Newark 7, N. J.

White's Cod Liver Oil Concentrate Tablets

One of White's Integrated Pediatric Vitamin Formulas

*U.S.P. Minimum Requirements

low incidence of uterine bleeding with the potent synthetic estrogen...

DIENESTROL

RECENTLY, Rakoff and co-workers* have observed that the incidence of uterine bleeding is significantly low when menopausal syndromes and related entities are treated with White's Dienestrol—a new, highly effective estrogen. In addition Dienestrol was found to be unusually well tolerated; clinical side effects are almost nonexistent.

Available: DIENESTROL TABLETS: 0.1 mg. (white) and 0.5 mg. (red) in bottles of 100 and 1,000.

AQUEOUS SUSPENSION OF DIENESTROL: In 10 cc. rubber-stoppered vials, 5 mg. of Dienestrol per each cc.

*Rakoff, A. E.; Paschkis, K. E. and Cantarow, A.: A Clinical Evaluation of Dienestrol, a Synthetic Estrogen, J. Clin. Endocrinol., 7:688-700 (Oct.) 1947.

White's

DIENESTROL

WHITE LABORATORIES, INC.,
Pharmaceutical Manufacturers, Newark 7, N. J.

When exposed to physiologic storms, patients suffering from adrenal cortex insufficiency must have the reserves needed to withstand the added stress. Functionally active adrenal cortices are a vital part of the protective mechanism under these circumstances. Lack of capacity to respond results in lowered resistance and increased susceptibility to infections.

Prompt, active supportive treatment with ADRENAL CORTEX EXTRACT (UPJOHN) fortifies general vitality, muscle tone and strength, helping to buttress the patient's progress and shorten convalescence.

ADRENAL CORTEX EXTRACT (UPJOHN) achieves high therapeutic effectiveness because it is a *natural complex*. It conveys the intricate multiple action of the whole cortical hormone.

Upjohn
KALAMAZOO 95, MICHIGAN
since 1886

Adrenal Cortex Extract (Upjohn)

Sterile solution in 10 cc. rubber-capped vials for subcutaneous, intramuscular, and intravenous therapy.

Old Age NEED NOT MEAN *Chronic Illness*

Clinical studies[1,2,3] demonstrate that the results of inadequate dietaries are insidiously cumulative and may not become evident for many years. Many of the afflictions of old age are now attributed to lifelong faulty dietaries and no longer need be the inevitable accompaniment of advanced years.

In advanced age the wisdom of dietaries high in vitamins, minerals, and protein, low in fat, and moderate in carbohydrate, is pointedly emphasized in reported clinical studies. Liberal amounts of vitamin B complex and of calcium, in particular, are important for increasing the appetite and for supporting the calcium integrity of the skeletal structure.

Ovaltine in milk, a delicious *multiple* dietary supplement, is highly useful in the management of aged patients. Its multiple vitamins, its important minerals, and its biologically complete protein are the very nutrients required for effecting full adequacy of even seriously faulty diets. The refreshing tastefulness and easy digestibility are welcomed by the aged.

The rich dietary contribution made by three daily glassfuls of Ovaltine in milk, is outlined in detail in the table.

[1] Boss, E.P.: The Physiologic and Clinical Phenomena of Aging, New Orleans M. & S. J. 97:64 (Aug.) 1944.

[2] Spies, T.D., and Collins, H.S.: Observation on Aging in Nutritionally Deficient Persons, J. Gerontol. *1*:33 (Jan.) 1946.

[3] Strieglitz, E.J.: Therapy of the Aged, M. Ann. District of Columbia *17*:197 (Apr.) 1948.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.

Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk, provide:*

CALORIES	676	VITAMIN A	3000 I.U.
PROTEIN	32 Gm.	VITAMIN B_1	1.16 mg.
FAT	32 Gm.	RIBOFLAVIN	2.0 mg.
CARBOHYDRATE	65 Gm.	NIACIN	6.8 mg.
CALCIUM	1.12 Gm.	VITAMIN C	30.0 mg.
PHOSPHORUS	0.94 Gm.	VITAMIN D	417 I.U.
IRON	12 mg.	COPPER	0.5 mg.

**Based on average reported values for milk.*

by far the most potent ORAL ESTROGEN available clinically

In exceedingly minute doses—as little as 0.02 mg. (1/3200 gr.) daily—ESTINYL* maintains the average menopausal patient free of symptoms. Even when initiating therapy and in the more severe cases, unusually small dosage—measured in hundredths of a milligram—has been found effective.

ESTINYL

(ETHINYL ESTRADIOL)

ESTINYL, a derivative of the ovarian follicular hormone, estradiol, evokes the sense of well-being characteristic of natural hormone therapy. It acts rapidly, often completely controlling climacteric symptoms within a few days. In therapeutic dosage side effects are notably infrequent. Unique response to minimal dosage permits effective estrogen therapy at low cost to patients.

DOSAGE: One ESTINYL Tablet (0.02 mg.) or one teaspoonful of ESTINYL LIQUID (0.03 mg.) daily, may be prescribed, reducing dosage as symptoms subside.

ESTINYL Tablets, 0.02 (buff) or 0.05 mg. (pink), in bottles of 100, 250 and 1000.

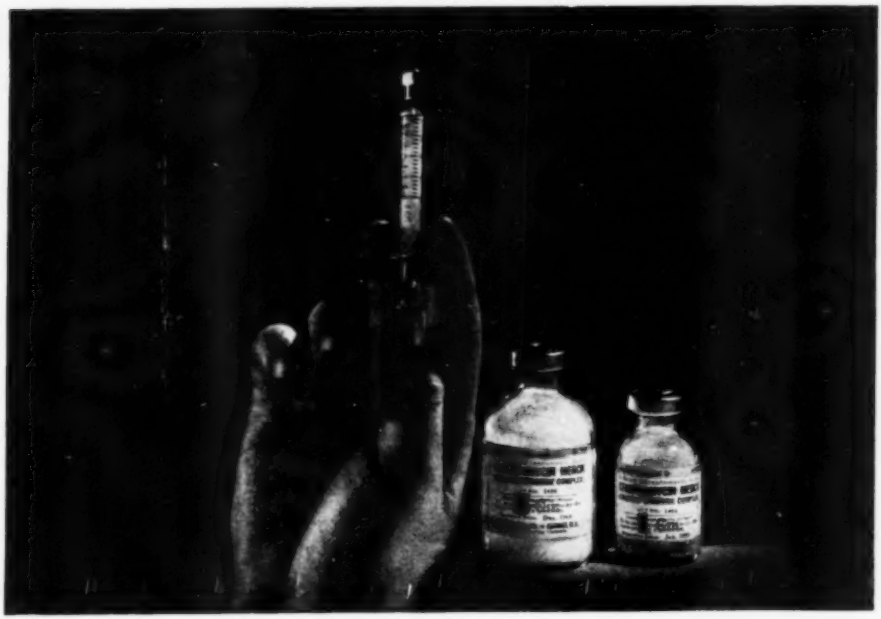
ESTINYL LIQUID, 0.03 mg. per 4 cc. (teaspoonful), in bottles of 4 and 16 oz.

*®

Schering CORPORATION • BLOOMFIELD, NEW JERSEY
IN CANADA, SCHERING CORPORATION LIMITED, MONTREAL

ESTINYL

SCHERING



To Facilitate Preparation of Solutions...

For greater convenience and economy, both important considerations, Streptomycin Calcium Chloride Complex now is supplied in a multiple-dose container, 5 Gm. in a 50 cc. vial.

DILUTION TABLE*

For Vials Containing the Equivalent of 1 Gm. or 5 Gm. Streptomycin Base (See Label)

Solvent added to 1-Gm. vial		Streptomycin base per cc.		Solvent added to 5-Gm. vial		Streptomycin base per cc.	
19 cc.	5.5 cc.	50 mg.	150 mg.	45.5 cc.	12 cc.	100 mg.	300 mg.
15.5 cc.	4.5 cc.	60 mg.	185 mg.	35.5 cc.	9.5 cc.	125 mg.	350 mg.
9 cc.	4 cc.	100 mg.	200 mg.	28.5 cc.	8 cc.	150 mg.	400 mg.
7 cc.	3 cc.	125 mg.	250 mg.	20.5 cc.	6.5 cc.	200 mg.	450 mg.
				15.5 cc.	5.5 cc.	250 mg.	500 mg.

For Streptomycin of the Highest Quality—Specify

STREPTOMYCIN

CALCIUM CHLORIDE COMPLEX

MERCK

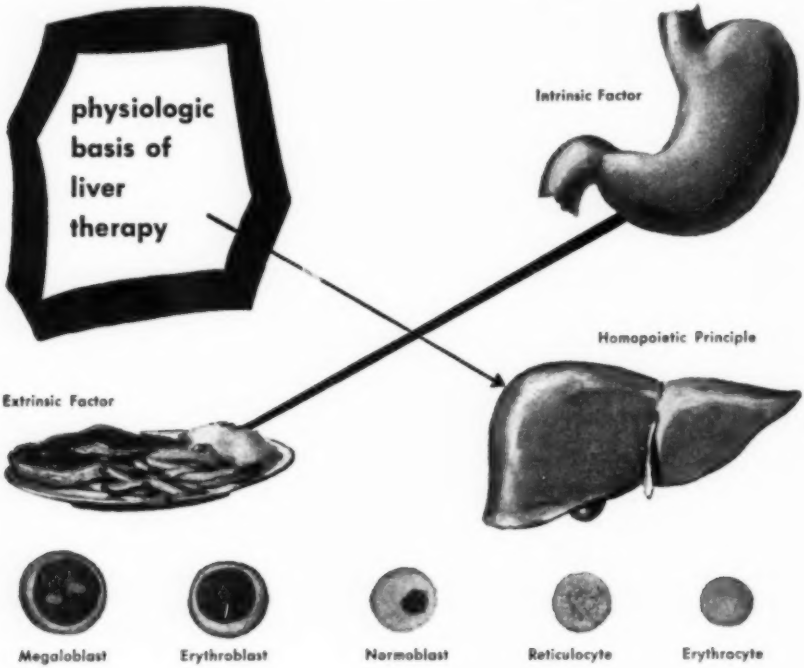
MERCK & CO., Inc. *Manufacturing Chemists* RAHWAY, N. J.

In Canada: MERCK & CO., Ltd. Montreal, Que.

* *Printed copies of this Dilution Table are available on request.*

MERCK MERCK

HABIT
TIME
ONE PINT
PKG. 1896
Wyeth
Petrogalar
Aqueous Suspension
of Mineral Oil
Plain
Active
Ingredient
Mineral Oil 65%
DIRECTIONS. Adults, one tablespoonful. Children over six years old, one teaspoonful. May be thinned with water, milk or fruit juice if desired.
CAUTION. To be taken only at bedtime. Do not use at any other time or administer to infants except upon the advice of a physician.
SHAKE WELL
Wyeth INCORPORATED - PHILADELPHIA - PA
1376374
Wyeth



According to Castle, the homopoietic principle in liver is a combination of an extrinsic factor derived from food and an intrinsic factor produced by the stomach. Liver Extract is also believed to contain certain secondary blood-building elements. Since the therapeutic properties of liver extracts vary widely, many failures in pernicious anemia therapy are reported due to the use of inert or deficient extracts.

Liver Preparations Armour

are carefully prepared to preserve the blood-regenerating, active constituents of the fresh liver. The finished extracts are carefully tested for therapeutic effectiveness on actual pernicious anemia patients in relapse.

Armour Liver Preparations

Liver Injection

2 U. S. P. Injectable Units per cc. (Crude.)

4 U. S. P. Injectable Units per cc.

Made from the unrefined 70% alcohol soluble fraction of liver extract in the manner described in the U. S. P. XIII for the preparation of Liver Injection (Crude.)

Liver Injection 2 U. S. P. units (Crude) (Armour) is available in 10 and 30 cc. rubber-capped vials.

Liver Injection 4 U. S. P. units (Armour) is available in 5, and 10 cc. rubber-capped vials.

10 U. S. P. Injectable Units per cc. in 1 cc., 5 cc., 10 cc., and 30 cc. rubber-capped vials.

15 U. S. P. Injectable units per cc. in 1 cc., 5 cc., and 10 cc. rubber-capped vials. A highly refined and concentrated preparation for massive dosage.

Solution Liver Extract—Oral

45 cc. equal 1 U. S. P. Oral Unit. A readily assimilable and therapeutically effective preparation for use when the oral route is indicated or preferred.

Liver Extract Concentrate—Capsules

9 capsules equal 1 U. S. P. Oral Unit. Odorless, tasteless. Sealed gelatin capsules in boxes of 50, 100.

Have confidence in the preparation you prescribe — specify "Armour"

ARMOUR *Laboratories*

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS

criteria in syphilotherapy

"Therefore, more than in any other disease, it is necessary in the treatment of an individual patient with syphilis to follow a therapeutic regimen which, after *long-term study* in *large series of patients*, has been established as *satisfactory* for the particular type of syphilis under consideration."*

MAPHARSEN®

an arsenical of choice in the treatment of syphilis

long-term study

More than a decade of clinical evaluation.

large series of patients

Over two hundred million injections already administered.

satisfactory

High therapeutic effectiveness with notable safety in causing disappearance of spirochetes, healing of lesions and reversal of seropositivity in a large percentage of cases.

MAPHARSEN (oxophenarsine hydrochloride, P. D. & Co.) is supplied in single dose ampoules of 0.04 Gm. and 0.06 Gm., boxes of 10, and in multiple dose ampoules of 0.6 Gm. in boxes of 10.

*Cecil, R. A.: A Textbook of Medicine. Philadelphia, W. B. Saunders Co., 1947, p. 878.

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

MEDICAMENTA VERA · P D & CO.

Visit the Parke-Davis Commercial Exhibit, Spaces 91, 92, and 93

With this in hand

The Cardiologist

is assured of

Dependability in Digitalis Administration

Being the powdered leaves made into
physiologically tested pills,
all that Digitalis can do, these pills will do.

Trial package and literature sent to physicians on request.

DAVIES, ROSE & COMPANY, Limited

Manufacturing Chemists, Boston 18, Massachusetts

Please Mention this Journal when writing to Advertisers

Tip from Tony

Many children put up a whale of a squawk when it comes to getting a haircut—much the same as when they're sick and forced to down bitter tasting medicine. In both instances, the power of the candy appeal offers an expedient solution. • Where oral penicillin therapy is indicated, for example, many physicians are prescribing *Dulcet* Penicillin Tablets, which look and taste so much like candy that children accept them as a treat. A cinnamon-flavored, sugar base disguises the bitterness of the penicillin, making the *Dulcet* Tablet cube practical for use either as a troche or for systemic effect. And *Dulcet* Penicillin Tablets are therapeutically sound. Each tablet contains 50,000 units of crystalline penicillin G potassium, along with 0.25 Gm. of calcium carbonate as a buffer. • Many of your adult patients, who dislike ordinary tablets, will welcome this pleasant way of taking oral penicillin. On your next prescription, insure patient acceptance by specifying *Dulcet* Penicillin Potassium Buffered Tablets. All pharmacies have them—in bottles of 12. ABBOTT LABORATORIES, North Chicago, Illinois.

Dulcet® Penicillin

POTASSIUM TABLETS (BUFFERED)

® (Medicated Sugar Tablets, Abbott)

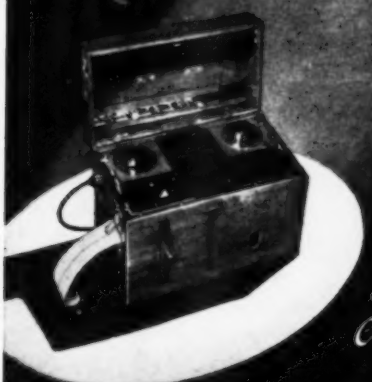
Only

IN THE DIRECT-WRITING

VISO

CARDIETTE

. . . WILL YOU BENEFIT BY THIS COMBINATION OF ELECTROCARDIOGRAPH ADVANTAGES . . .



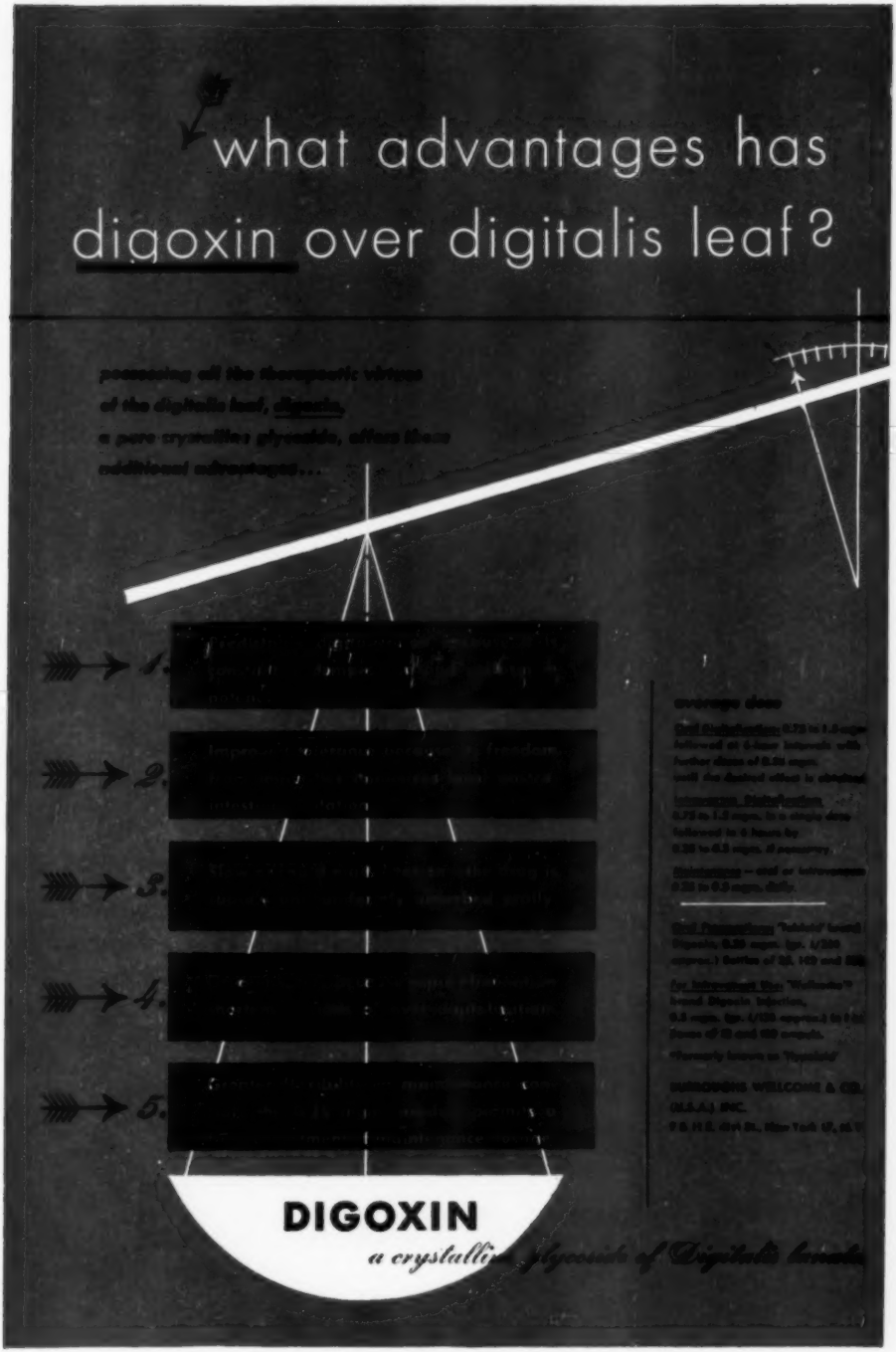
Standard 'cardiograms
Assurance of accuracy
Modern, simplified design
A background of experience
Nationwide acceptance
Complete service by the maker

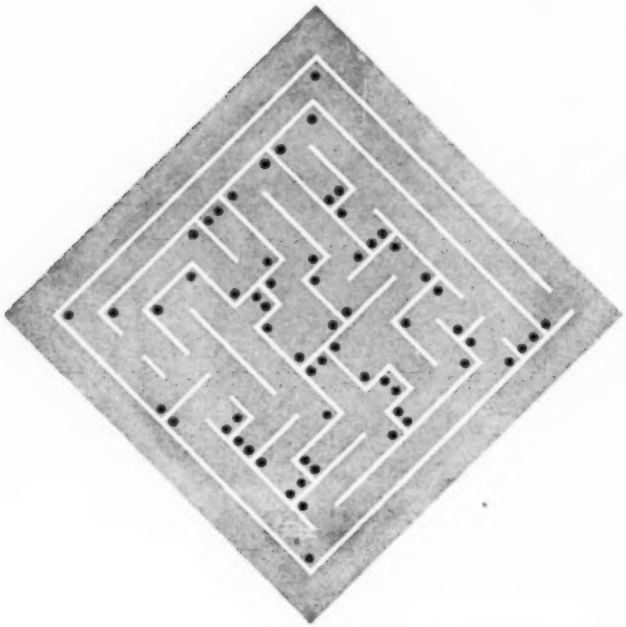
ACCEPTED COUNCIL ON PHYSICAL MEDICINE AMERICAN MEDICAL ASSOCIATION

SANBORN COMPANY

CAMBRIDGE 39, MASSACHUSETTS

Offices in New York, Philadelphia, Baltimore, Washington, Cleveland, Detroit, Chicago, Atlanta, Miami, New Orleans, Dallas, St. Louis, Minneapolis, Denver, Los Angeles, San Francisco, Seattle.


what advantages has
digoxin over digitalis leaf?
DIGOXIN



in every corner Penicillin products bearing the Lilly label are easy to obtain.

Complete assortments are maintained by most of the drug stores and hospitals located in every corner of the nation. Your pharmacist, in turn, can easily replenish stocks from near-by drug wholesalers. No other nationally distributed pharmaceutical products may be obtained more quickly and easily than those bearing the Lilly label.

Penicillin—G, Crystalline-Potassium, is available in ampoules, ointment, ophthalmic ointment, tablets, and troches. Complete literature is available to physicians upon request.

ELI LILLY AND COMPANY

Conquest of pain IN CHILDBIRTH

Particularly in obstetrics, the power of DEMEROL hydrochloride to allay pain, usually without depressing respiration or endangering mother or child, is of the highest order of significance. DEMEROL hydrochloride is a specific for *pain.*

Average adult dose: 100 mg.

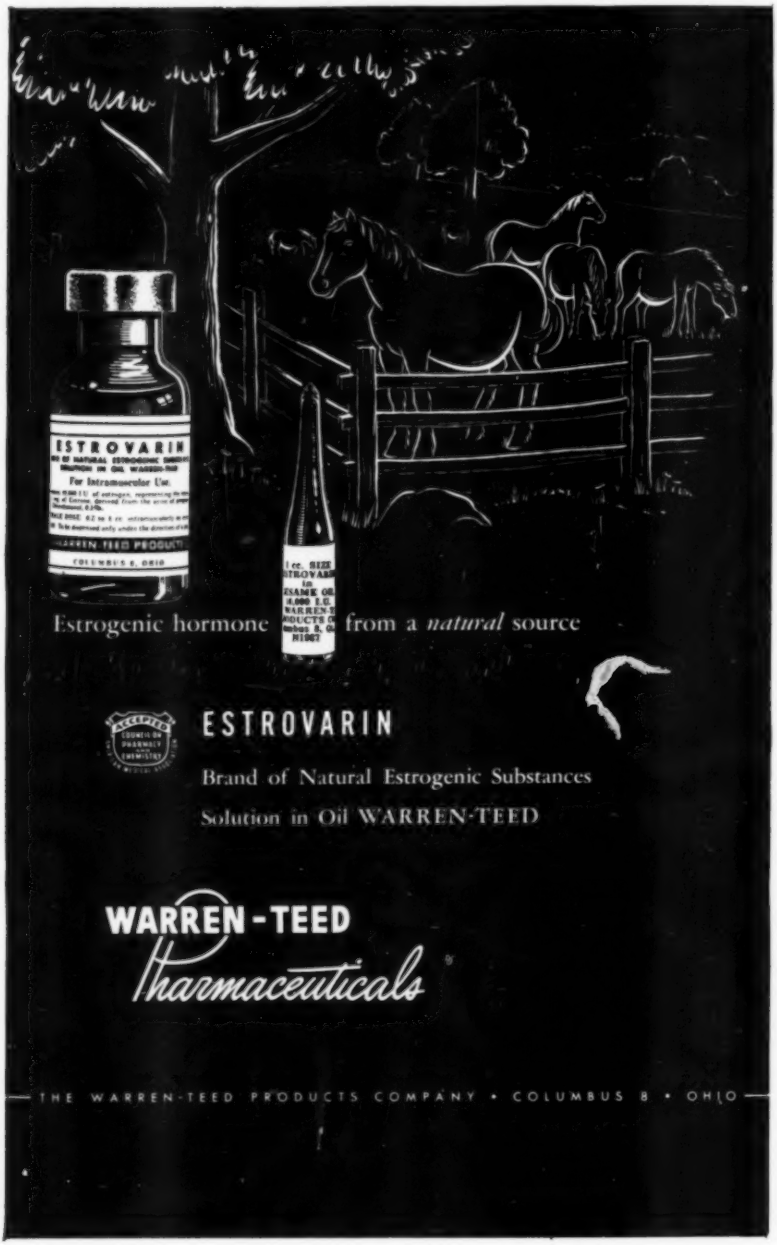
Ampuls of 2 cc. (100 mg.); vials of 30 cc. (50 mg./cc.); tablets of 50 mg. and 100 mg.

DEMEROL®
HYDROCHLORIDE

WARNING: May be habit forming. Narcotic blank required.

Winthrop-Stearns INC.
NEW YORK 13, N. Y. WINDSOR, ONT.

Demerol, trademark reg. U. S. & Canada, brand of meperidine (isonipecaine) hydrochloride.



VISIT OUR EXHIBIT—BOOTH No. 15—AT YOUR ANNUAL SESSION

Important advance in blood banking

BAXTER

"Fuso-Flo"

STOPPER

Since Baxter introduced the closed system, the Fuso-Flo stopper is the most important new step in making blood and plasma infusions trouble-free. This exclusive Baxter feature provides efficient preliminary straining, prior to filtration. It assures proper, uninterrupted flow regardless of condition or age of blood or plasma. Fuso-Flo is another example of continuing Baxter research and development in parenteral therapy. No other method is used in so many hospitals.

Manufactured by
BAXTER Laboratories
Morton Grove, Illinois Acton, Ontario

Produced and distributed in the eleven western states by DON BAXTER, Inc., Glendale, California

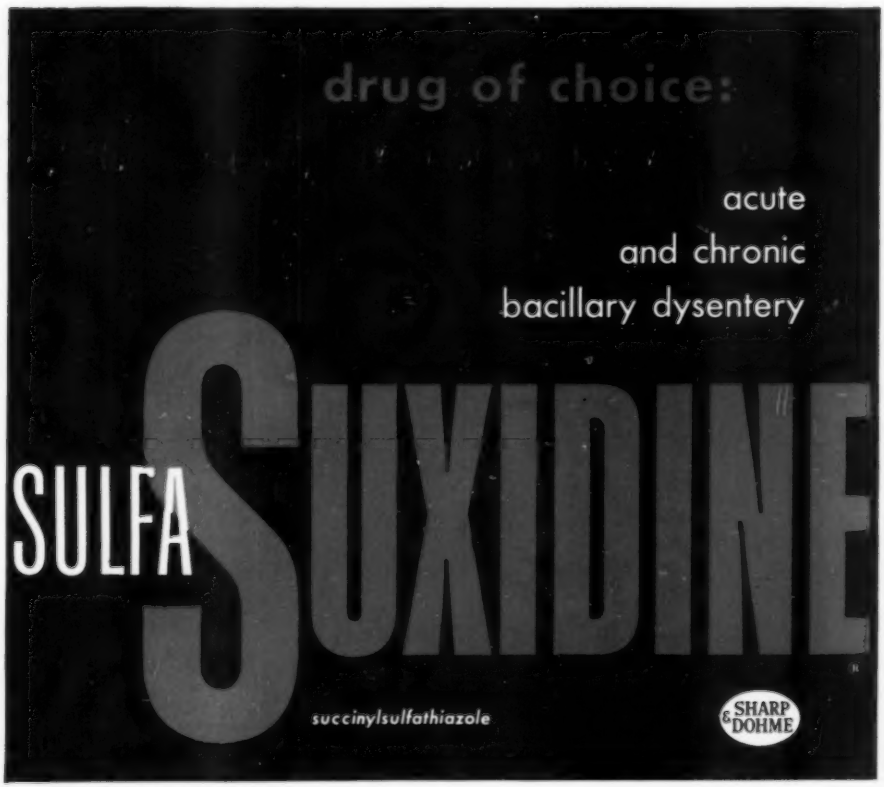
AMERICAN HOSPITAL SUPPLY CORPORATION
DISTRIBUTORS EAST OF THE ROCKIES • GENERAL OFFICES: EVANSTON, ILLINOIS

SULFASUXIDINE

SULFASUXIDINE[1] *succinylsulfathiazole* is considered a drug of choice in treatment of acute and chronic bacillary dysentery, including the carrier states of this disease[2]. SULFASUXIDINE *succinylsulfathiazole* is also exceptionally useful as a prophylactic agent prior to intestinal surgery, as well as postoperatively to speed convalescence, and has proved highly effective for control of ulcerative colitis and *E. coli* infections of the genito-urinary tract. Toxic reactions are negligible. Only about 5% of the drug is absorbed from the bowel and is rapidly excreted by the kidneys. Blood concentrations are extremely low.

SULFASUXIDINE *succinylsulfathiazole* is supplied in 0.5-Gm. tablets, bottles of 100, 500, and 1,000; powder (also for oral administration) in ¼-lb. and 1-lb. bottles . . . Sharp & Dohme, Philadelphia 1, Pa.

1. Reg. Trademark, Sharp & Dohme 2. J.A.M.A. *128*:1152, 1945



Correction

On page 816 of the November 1948 issue of the ANNALS ("Experimental and Clinical Therapeutic Studies on Lymphosarcoma" by C. P. Rhoads) is the statement that "P^{32} is an emitter of gamma radiation." This is an error. P^{32} is a pure "beta" emitter.

ANNALS OF
INTERNAL MEDICINE

VOLUME 30 FEBRUARY, 1949 NUMBER 2

DIAGNOSTIC SIGNIFICANCE OF URINARY HORMONAL ASSAYS: REPORT OF EXPERIENCE WITH MEASUREMENTS OF 17-KETOSTEROIDS AND FOLLICLE STIMULATING HORMONE IN THE URINE *

By ROBERTO F. ESCAMILLA, M.D., F.A.C.P., *San Francisco, California*

HISTORY

THE discovery that extracts of human urine have measurable androgenic and estrogenic effects has stimulated many investigators. Concepts worked out by years of clinical observations seemed possible of more definite proof or disproof. Estimating the values of excretion products of endocrine function in the urine promised a way to study further these established clinical syndromes in the human patient rather than in the experimental animal.

However, bioassay is necessary in many of the determinations. This usually means maintaining animal colonies with all the attendant complications, and the necessity for specially trained personnel. Also various animal species do not react alike to similar stimuli and of course results are not always transferable to humans. All of these factors have limited the widespread acceptance and availability of many of the tests for clinical use—with the obvious exception of the pregnancy tests.

However, with the introduction of a chemical test in which animals were not necessary and in which a color reaction gave a sensitive end-point, there was renewed and more general interest in measuring urine hormone excretion. The test alluded to is that for steroids, introduced by Zimmermann in 1935 [1] as a test for "androgens." He showed that substances with an active methylene group (CH_2CO) produced a red color with meta-dinitrobenzene and KOH which may be measured quantitatively. 17-Ketosteroids, that is,

* Presented before the Twenty-ninth Annual Session of the American College of Physicians, San Francisco, California, April 21, 1948.

From the Division of Medicine, University of California Medical School, San Francisco, California.

Copyright, 1949, by The American College of Physicians

steroids with a ketone group at the 17th carbon atom, produce this color reaction. Estrone is a 17-ketosteroid but can be excluded from the test by washing out the acid phenolic fraction with alkali. The neutral 17-ketosteroids which remain, and which are measured, are primarily the excretion products of testosterone and certain adrenal steroids. Further subdivision of this fraction may yield additional clinical information, as will be shown. One obvious drawback is that not all 17-ketosteroids are androgens, nor are all androgens 17-ketosteroids, so the test is not one for androgens as such. However, it generally parallels the biologic test and is obviously much easier to set up and perform than the latter which involves measuring the growth of a capon's comb.

Since the adrenal cortex is thought to produce androgenic steroids in both men and women, the test is now considered an indication, though not a true measure, of the combined activity of the adrenal cortex and the testes in the male, and, in the female, of the adrenal cortex alone. Since both the adrenal cortex and the testes are under control of the pituitary, the test may be considered to be an indirect measure of the function of that gland. The above concept has been very well presented by Ingram.[2]

Tests Now Used

The following is a general review of what is being done in this field at the present time, and some of the tests that are being carried out in various laboratories are described. It will be noted that most are biological assays, but it is the belief of the author that the increased availability of the chemical test for 17-ketosteroids has stimulated more general investigation and the use of many of the other tests.

Follicle Stimulating Hormone (*FSH*). This pituitary gonadotropin has also been known as prolan A, thylakentrin and pituitary gonadotropin A. A method for assay was first described by Zondek[3] in 1930 and has more recently been reviewed and modified by Klinefelter, Albright and Griswold.[4] In their method the hormone is precipitated from the urine with alcohol, washed with alcohol and ether, dried in a desiccator, diluted with distilled water and then injected subcutaneously into immature female white mice for three days. The result is considered positive when the uterus is enlarged (to over 7 mg.). After dilutions and calculations they found normal men and women to excrete from 6.6 to 53 mouse units per 24 hours.

A method using rats is preferred by some workers and a recent publication on this subject by Jungck, Maddock and Heller[5] also reports the advantages of ultra-filtration over the alcohol-precipitation dialysis in preparing the urine concentrate for injection. They report that this modification makes the test less complex, less time-consuming and less expensive. The urine concentrate is injected into female rats once every 12 hours for six injections. Twenty-four hours after the last injection the uterus and ovaries are removed and weighed, and the weights recorded as end-points.

The first method using mice and recording results in mouse units seems to be most generally used at present. It is claimed to have the advantage of a more definite end-point. If a high concentration of FSH is present, the modification (using mouse units) of Smith, Albright and Dodge[6] is widely used.

It should be kept in mind that if a woman is menstruating regularly her gonadotropins will be normal, and there will be no need to run this test to ascertain any possible high or low levels.

Various other pituitary hormones can be assayed in urine. These include:

Interstitial-cell stimulating hormone—also called luteinizing hormone or metakentrin (ICSH, LH). This is tested for in hypophysectomized rats causing, in the female, restoration of the involuted interstitial or "wheel" cells in the ovaries, and in the male, an increase in weight of the ventral prostate (Simpson, Li and Evans, 1942[7] and Greep, Van Dyke and Chow, 1941[8]).

The lactogenic hormone—(also known as prolactin, galactin, or mammotropin) can be assayed in pigeons by measuring the effect on the weight of the crop sac (Riddle, Bates, Dykshorn, 1933[9]). A later method reported by Lyons and Page[10] accomplishes the test by intradermal injections over the crop sacs of squabs. It is reported to be more sensitive, and to detect the hormone in doses of 1 microgram.

The adrenocorticotropic hormone (ACTH)—is tested for in hypophysectomized female rats, starting injections 14 days after operation and measuring the amount of repair which takes place in the involuted adrenals. An adrenal maintenance test is also used, starting injections in male rats immediately after the hypophysectomy and noting maintenance of adrenal weight after two weeks of injections (Simpson, Evans and Li, 1943[11]). Another test for the adrenocorticotropic hormone is based upon the observation by Sayers, Sayers, Liang and Long[12] that its injection into rats and guinea pigs is followed by a prompt fall in adrenal ascorbic acid, and a slower fall in adrenal cholesterol. It is suggested that these changes are associated with the formation and release of the adrenal cortical hormones.

Thyrotropic hormone—commonly tested for with the guinea pig in which injections of the hormone will cause doubling in weight of the thyroid (Rowlands and Parkes, 1934[13]). Another method has been suggested by De Robertis, at first alone and later with Del Conte.[14, 15] They noted that injections of the thyrotropic hormone caused an increased formation of intracellular colloid droplets in thyroid epithelium. Recording the number of these droplets was suggested as a method of assay and was reported as being extremely sensitive—detecting as little as 0.0002 Junkmann-Schoeller units. At first the rat was used and later, the guinea pig. More recently Dvoskin[16] reported trying this method in the chick, also recording thyroid weight and thyroid-epithelium cell-height. He concluded that this was not

as sensitive as the test using the guinea pig, but pointed out that more direct comparisons were needed.

In general, the tests for thyrotropic hormone are not yet considered to be completely satisfactory.

Growth hormone—can be bioassayed by noting the microscopic effect of injections on the width of the epiphyseal cartilage plate in the tibia of the hypophysectomized female rat (Evans et al., 1943 [17]). So far this test has only been used with pituitary extracts.*

The posterior pituitary hormones, vasopressin and oxytocin can also be tested for, but the tests are not considered completely reliable or specific. Vasopressin can be measured by the pressor effect in anesthetized dogs, while oxytocin is measured by its effect in causing contractions of an isolated guinea pig uterus suspended in Locke-Ringer solution and attached to a kymograph. In both methods, comparisons are made with a measured amount of standard dried pituitary powder (Kamm, et al.[18]).

It will be noted that nearly all of these are biological assays. They are being done principally in centers where there is particular interest in investigation in endocrinology.

The *pregnancy tests* usually depend upon the increased excretion of chorionic gonadotropin.

The *Aschheim-Zondek* and *Friedman* tests are well known and widely used. The former utilizes immature mice and the latter a rabbit for the test animal.

More recently, Guterman [19, 20] has reported a pregnancy test which measures pregnandiol in the urine, using a color reaction. This can be done in 3 hours and he reports it to be accurate in 90 per cent of the cases tested. Pregnandiol is the excretion product of progesterone and the test is based upon the increased activity of the corpus luteum and later the placenta during pregnancy. Since desoxycorticosterone acetate also gives rise to pregnandiol, adrenal cortical hyperplasia or tumor may give a false reaction. However, Reinhart and Barnes [21] have recently reported an error of 25 per cent in both positive and negative series using this test. Mack and Parks [22] have also used increased pregnandiol excretion as a pregnancy test. They measured the amount of unpurified pregnandiol that could be precipitated from the urine.

Other tests can be mentioned, such as that using the *South African clawed frog* (*Xenopus laevis*), originally described by Shapiro and Zwarenstein.[23] This depends upon the extrusion of ova within 24 hours after injection of pregnancy urine extracts into the dorsal lymph sac of the female. Another method uses the *male toad* (*Bufo arenarum* Hensel). It has been described by Galli-Mainini of Buenos Aires.[24] In this test 10 c.c. of urine is injected into the lateral lymph sac of the toad. Three hours later urine is collected from the toad by introducing a pipette into the anal canal. A drop is ex-

* Recently Kinsell et al.,[94] in a communication now in press, reported measurement of growth hormone in plasma by this method.

amined under the microscope and if spermatozoa are present, the test is positive. An accuracy of 95 per cent is reported and it is considered rapid and economical. The same toad can be used again after an interval of one week. The test is widely used in South America. In a more recent communication from this country, Robbins and Parker [25] report the use of the male North American frog (*Rana pipiens*), in a similar manner.

Adrenal cortical hormones also appear in the urine and many steroids have been isolated (Dorfman and co-workers, and Browne and co-workers—references given in Jr. Clin. Endocrin., Editorial [26]). One particularly active group of compounds are those with an oxygen atom at C11 on the steroid skeleton.

A *biological test* for the cortical hormones having a glycogenic action was described by Venning, Kazmin and Bell [27] in 1946. It is based upon the fact that the adrenalectomized animal does not deposit glycogen in the liver. The authors measured the effect of 11-dehydro-17-hydroxy-corticosterone, and 11-dehydro-corticosterone and found the former to be three times as active as the latter. The clinical test measures both and is accomplished by extracting a 48-hour specimen of urine. The dried extract is diluted with 10 per cent alcohol in 5 per cent glucose and injected into six to eight male white mice. The mice have been adrenalectomized four days before and given measured concentrations of glucose and saline. Seven injections of the urine extract are given at intervals of 45 minutes and one hour, and an hour after the last, the mice are anesthetized and the livers removed and assayed for glycogen content. The amount of glycogen taken up is in proportion to the glycogenic corticoids in the urine sample. The test has been used considerably in Montreal and Venning and Browne [28] have reported that the normal male excretes 40 to 85 glycogenic units per 24 hours (average 60) and the normal female excretes 25 to 55 glycogenic units per 24 hours (average 39). In Addison's disease and panhypopituitarism they reported the values to be low or not detectable; in anorexia nervosa the values were normal or slightly low; in simple hirsutism the values were normal. However, there was a marked increase in three out of four cases of Cushing's syndrome (males 386 and 42—females 340 and 137 Gl. u./24 hours). The authors felt that in the one instance with a normal value, the disease was in an arrested state. Four cases of acromegaly were tested. Three chronic cases were normal and one recent active case in a male showed a high level (134 Gl. units). Values did not always parallel the 17-ketosteroids.

Later studies by Venning and Browne [29] showed that therapy with testosterone propionate and methyl testosterone generally caused a reduction in the excreted glycogenic corticoids. In the same group of cases, the 17-ketosteroids decreased under therapy with methyl testosterone, but not with testosterone propionate.

Results of use of a colorimetric method for measurement of the 11 oxycorticosteroids has been reported by Talbot, Albright, Saltzman, Zygmuntowicz and Wixom.[30] The method had been previously described by Talbot,

Saltzman, Wixom and Wolfe.[31] The substances measured were thought to correspond to adrenal cortical steroids with a ketone or hydroxyl group at the 11th carbon atom, a two carbon sugar-like ketolic side chain and an hydroxyl group attached to the 17th carbon atom. Five of these 11-oxy compounds could be separated for the assay by their differential solubility in benzene and water.* They promote sugar metabolism and have been called the "S" hormones. They are probably similar to and roughly parallel to the glycogenic corticoids measured biologically by Venning and Browne in the test described above.

The results reported on 24-hour urines showed values in normal individuals of both sexes to be from 0.1 to 0.44 mg. per day, with an average of 0.22 mg. In 17 patients with hypoadrenocorticism the output was slightly lower, ranging from 0.02 mg. to 0.29 mg. per 24 hours with an average of 0.14 mg. Two patients with myxedema had low values (below 0.1 mg.). In one case, this rose to normal under treatment with thyroid. They reported that in panhypopituitarism the value was under 0.18 mg. in six out of seven cases. Five cases of adrenal virilism with high 17-ketosteroids were studied and the values for 11-oxycorticosteroids were normal or only slightly elevated. Excretion was studied in 12 patients with Cushing's syndrome and the values were high (0.6 to 12.0 mg. per 24 hours). The values were reduced in two of the patients by testosterone therapy. Three other cases in remission showed normal values. Non specific trauma (burns) showed similar high figures. The value fell to normal in one patient three days before death (thus fitting the theory of the adaptation syndrome of Selye).

Urinary excretions of the *estrogens*, alpha estradiol, estrone and estriol have been measured by *biological methods*. One such is that reported by Smith, Smith and Schiller.[33] In this method a 24- or 48-hour urine is subjected to hydrolysis and then extracted to separate the "strong" phenolic fraction containing the estriol and the "weak" phenolic fraction containing the estrone. The actual method of bioassay was described in another paper (Smith, Smith and Pincus[34]) and utilized spayed female rats in a diestrous state. Three injections of the extract were given four hours apart and a vaginal smear taken 48 hours after the first injection. The smear was considered positive if it showed a pre-estrous, full estrous, or post-estrous phase, and the smallest amount causing a positive result in four out of six rats was considered one rat unit. They also tried *colorimetric determinations*, but the fractions showed large over-estimates due to the presence of inactive chromogenic material.

However, a new fluorometric method has appeared which shows promise of greatly simplifying urinary estrogen assays. Jailer[35] outlined a procedure for extraction using H_2SO_4 and methyl alcohol, then reading the result in a Coleman Photofluorometer at wave lengths of 4360 Å and 3650 Å. He recorded concentrations of estrone, estradiol, and estriol and reported a con-

* A modification of this test has more recently been reported by Daughaday, Jaffe and Williams.[32]

stant 50 to 60 per cent recovery of known amounts of the substances in recovery experiments. Cohen and Bates [36] have reported a somewhat similar method using H_2SO_4 and ethanol, then reading the resulting red color (Kober reaction) in a photometer at a wave length of 5100 Å. The relative simplicity of these methods is extremely appealing and it is hoped that wider experience will evaluate their specificity.

Pregnandiol, which is the excretion product of progesterone, can also be measured in the urine. Venning and Browne in 1936 [37] isolated it as the water-soluble compound, sodium pregnandiol glucuronidate. In 1937 Venning [38] was convinced of its identity and published a detailed method for its measurement. Urine is extracted with butyl alcohol and the residue treated so that a crystalline substance results which can be weighed. It has a melting point of 267 to 271° C. which is specific for sodium pregnandiol glucuronidate. Use of a conversion factor (0.597) easily gives the amount of pregnandiol.

A *colorimetric method* for determination of pregnandiol suggested by Guterman [19, 20] has already been discussed above under "pregnancy tests." As noted, there is still some discussion as to its specificity.

The *androgens* can be assayed *biologically* by measuring the effect of injections of material to be tested on the size of a capon's comb. A capon unit is considered the amount which, after six consecutive daily injections, will cause a 20 per cent average increase in the weight or area of the comb (Funk, Harrow and Lejwa, 1929 [39, 40] and Tschopp, 1935 [41]). Other methods of bioassay involve the effects on chick combs, stimulation of seminal vesicles, prostate and preputial glands in rats and mice, causing growth of a masculine "sword" in a female swordfish, and stimulating the clasping reflex in frogs (Selye [42]).

However, the test that has stimulated the widest interest and is now more generally available is that for 17-ketosteroids previously mentioned. This is a chemical test, depending on the Zimmermann [1] color reaction for its endpoint. While all 17-ketosteroids are not androgens and all androgens are not 17-ketosteroids, the values generally parallel the results of bio-assays for androgens, and accumulated experience has indicated that the test has considerable clinical value. It should be remembered that in men the androgens (and eventually the excreted 17-ketosteroids) originate in both the testes and the adrenal cortices, and in women they apparently come from the adrenal cortices alone.

In 1941 Fraser, Forbes, Albright, Sulkowitch and Reifenstein [43] reported a method that has been widely used. They collected 16-hour (two overnight) specimens, but corrected the figures to excretion per 24-hours.* The

* Later Pincus [44] showed that night values for 17-ketosteroids were regularly lower than day values, and Forbes et al.[45] in 1947 also noted this, but thought that the lower night levels were more constant. They suggested collecting two overnight specimens in order to estimate the "basal ketosteroid excretion." However, the common practice at present is to estimate the excretion using a 24-hour urine specimen.

specimens were preserved with 10 c.c. of concentrated HCl. Hydrolysis, ether extraction and purification were done by the combined hydrolysis and extraction method of Callow, Callow, Emmens and Stroud.[46] In this, concentrated hydrochloric acid and carbon tetrachloride were added to the urine and boiled for two hours. The carbon tetrachloride was sucked out and the same extraction for two-hour periods was repeated twice more. The carbon tetrachloride was then distilled off and the residue taken up in benzene. This was fractionated by washing twice with sodium bicarbonate solution and then the mixture was freed from phenols by extracting five times with 2N sodium hydroxide. The benzene solution was evaporated to dryness and extracted four to five times with re-distilled ether. It was then filtered through sintered glass and the filtrate evaporated in a stream of nitrogen. The residue was taken up in absolute alcohol and was then suitable for colorimetric assay. This was done using a photoelectric colorimeter following directions previously published by Callow, Callow and Emmens.[47]

The 1941 paper by Fraser et al.[48] submitted the results of over 1500 assays by their method, which they reported as accurate to 10 to 20 per cent (1 to 2 mg. of sterone per 24 hours). Their normal ranges of total neutral 17-ketosteroids for adult males varied from 8.1 to 22.6 mg. per 24 hours with an average of 13.8 mg., and in adult females, the range was from 5.1 to 14.2 mg. with the average of 9.0 mg. per 24 hours. The values were lowered in old age and also in malnutrition, anemia, infection, and especially in liver disease. In five female patients with Addison's disease, the assays approximated zero, as they did in 15 cases of panhypopituitarism. High assays were present in patients with adrenal tumor or hyperplasia. Cushing's syndrome with adrenal tumor also showed high values. Three patients without tumors showed high or high normal assays. One patient with arrhenoblastoma and one with disgerminoma showed normal levels. Male eunuchoidism and hypothyroidism showed low levels. They noted that about 50 per cent of testosterone propionate injected was recoverable in the urine as 17-ketosteroids.*

In a review on the subject in 1942, Talbot and Butler [52] concluded that the test did provide diagnostic information and was particularly helpful in detecting hyper- and hypofunction of the adrenal cortex, and hypofunction of the thyroid and pituitary glands.

Many modifications of the test have appeared and are still appearing e.g.

* Before this time, Callow, Callow and Emmens in 1939 [46] had noted that testosterone propionate in doses of 50 mg. per week and up caused an increase in the urinary 17-ketosteroids. Later, Frame, Fleischmann and Wilkins [49] reported that both testosterone propionate and unesterified testosterone caused such an increase, while methyl testosterone did not. Reifenstein, et al. in 1945 [50] also noted the increase following administration of testosterone propionate and reported that following methyl testosterone there was an actual depression of 17-ketosteroid output in normal patients, and also in patients with Cushing's syndrome and adrenal hyperplasia. Cuyler et al. in 1942 [51] reported that the administration of desoxycorticosterone acetate did not cause any constant alteration in 17-ketosteroid output in normal adults.

a more rapid method of extraction by refluxing for 10 minutes with boiling CCl_4 was suggested by Robbie and Gibson [53] in 1943 and was reported to show a variation of ± 10 per cent or less. Wooster [54] also presented a simplified method and compared some of the previously reported technics. Another publication comparing previous methods appeared in 1943 by Nathanson and Wilson.[55] They stressed the importance of the adjustment of reading times in the color reaction to make for closer agreement between the various methods. Friedgood, Taylor and Wright [56] compared methods of extraction and hydrolysis and concluded that ether-toluol extraction was superior to that with CCl_4.

The most recent rapid method appeared in 1947, reported by Drekter, Pearson, Bartczak and McGavack.[57] They reported that their method could be done in three hours and could easily be adapted to small volumes of urine.

The end-point for the above methods is the total neutral 17-ketosteroids and this is as far as most laboratories carry the test for clinical purposes.

However, other investigators have devised methods to further sub-divide the ketosteroids in the hope of eliciting variations in concentration of individual compounds, or groups of compounds, which might have some clinical importance. Talbot, Berman, MacLachlan and Wolfe [58] used Girard's reagent "T" to separate the ketonic and non-ketonic fractions of the neutral steroids. They found the non-ketonic fraction to contain pregnandiol. The ketonic fraction was then divided into alcoholic and non-alcoholic partitions and the alcoholic portion further divided into alpha and beta fractions with digitonin.

Werner [59] has reported that the non-ketonic fraction contains 10 to 15 per cent of the 17-ketosteroids and that this proportion is fairly constant.

The alpha and beta separation with digitonin was published by Baumann and Metzger in 1940.[60] They found that the beta fraction which precipitates with digitonin was usually 5 per cent or less, though it could be up to 15 per cent in men between the ages of 20 and 27. However, in one case of adrenal cortical carcinoma it was increased to 40 per cent of a total 17-ketosteroid assay of 350 mg. Salter, Cahen and Sappington [61] reported further on this in 1946, and noted that the normal daily averages for the fractions were as follows: male adults—alpha 12.9 mg.; beta 1.3 mg.; female adults—alpha 6.3 mg.; beta 1.3 mg. The ratio of alpha to beta was reported as 9:1 in normals, while in eunuchoidism it was 2:1, in virilism without tumor 3:1, and in virilism with tumor 1:2. The elevation of the beta fraction in adrenal cortical carcinoma was therefore particularly striking. They also noted that the proportion of the beta fraction might be high, even without elevation of the total 17-ketosteroids, in amenorrhea with virilism.

In a review of the subject in 1943, Pincus [62] listed the following as the principal urinary 17-ketosteroids with some of their characteristics:

(1) *Estrone*—eliminated in removing the phenolic fraction by treating with strong alkali during the extraction.

(2) *Androsterone*—alcoholic alpha ketosteroid—0.1 mg. equals 1 international unit of androgenic activity. Probably from testosterone.

(3) *Etiocholanol—3 alpha—17—one;* alcoholic alpha ketosteroid—inactive biologically. Probably from testosterone.

(4) *Isoandrosterone*—alcoholic beta ketosteroid, 0.1 mg. equals 0.12 international units androgenic activity.

(5) *Dehydroisoandrosterone*—alcoholic beta ketosteroid, 0.1 mg. equals 0.33 international units androgenic activity. Probably from the adrenal. (This is more available and is now being used most frequently as a standard for colorimetric comparison.)

(6) *Androsterone 17*—non-alcoholic 17-ketosteroid, 0.1 mg. equals 0.8 international units androgenic activity.

(7) *Delta* ^{3,5} *androstadienone*—non-alcoholic 17-ketosteroid.

A new chromatographic-colorimetric method of fractionation has been reported by Dingemanse, Veld and de Laat.[63] In this method, after some preliminary chemical purification of the urine, the extract is dissolved in carbon tetrachloride, benzene or ethanol. It is then passed through a standardized column of Al_2O_3. The eluate is withdrawn in several fractions, and the 17-ketosteroids measured separately. They were able to separate eight fractions, starting with only 500 c.c. of urine.

This method is now being used considerably in research starting with large volumes of urine. Recently Lieberman, Dobriner, Hill, Fieser and Rhoads[64] reported analyses of ketonic fractions that had been separated into alphahydroxy (not precipitated by digitonin) and beta hydroxy (precipitated by digitonin) groups. They encountered 35 different substances in the alpha group and seven compounds in the beta group. The individual compounds were identified by infra-red spectrophotometry. Of the 35 alpha-ketosteroids, they reported complete identification of 22 of the compounds and incomplete identification of 13 (nine by melting points alone and four by melting points and C & H analyses). In the group of seven beta-ketosteroids, four were completely identified and three partially identified (one by melting point alone and two by melting points and C & H analyses). The completely identified 17-ketosteroids are listed in table 1.

It should be restated that the above represents late experimental work which is of a fundamental nature. The importance will have to be evaluated when wider experience is reported. However, some of these compounds apparently are found only in certain disease states.

Separation of steroids by paper partition chromatography has recently been reported by Burton, Zaffaroni and Keutmann.[65] While clinical studies using this method of fractionating 17-ketosteroids in urine or other biological material have not yet been reported, the method offers great promise. Attempts to adapt the procedure for clinical use are now in progress (Arrick, M., Gordan, G. S., and Elliott, H. W.—personal communication).

TABLE I

Urinary alpha 17-ketosteroids after Lieberman, Dobriner, Hill, Fieser and Rhoads—1948[44]

1. delta 3,5-Androstadienone-17
2. delta$^{2(or\ 3)}$-Androstenone-17
3. 3-Chloro-delta^{5}-androstenone-17
4. Etiocholanol-3 alpha-one-17 acetate-3
5. delta^{11}(?)-Androstenol-3 alpha-one-17 acetate-3
6. Androsterone acetate
7. Allopregnanedione-3,20
8. Pregnanedione-3,20
9. Androstanedione-3,17
10. Etiocholanedione-3,17
11. delta^{4}-Androstenedione-3,17
12. Allopregnanol-3 alpha-one-20
13. Pregnanol-3 alpha-one-20
14. Androsterone
15. delta^{5}-Androstenol-3 alpha-one-17
16. 17-Isopregnanol-3 alpha-one-20
17. delta^{5}-Etiocholenol-3 alpha-one-17
18. Etiocholanol-3 alpha-one-17
19. Androstanediol-3 alpha, 11 beta-one-17
20. Etiocholanol-3 alpha-dione-11,17
21. Pregnanediol-3 alpha, one-20
22. Allopregnanediol-3 alpha, 6-one-20

Urinary beta 17-ketosteroids

1. delta$^{2(or\ 3)}$-Allopregnenone-20
2. Allopregnanol-3 beta-one-20
3. Allopregnanol-3 beta-one-20
3. Dehydroisoandrosterone
4. Isoandrosterone

TESTS GENERALLY AVAILABLE

As noted before, many of the tests described above are being performed only in centers where research in endocrinology is in progress. However, some are available away from such centers, and such availability seems to be increasing.

Perhaps the most widely used are the pregnancy tests, with the Aschheim-Zondek and the Friedman tests being the most frequent. It should be recalled that these are also positive in patients with chorionephithelioma and in hydatidiform mole. The Galli-Mainini (toad) test [24] has been reported to be in general use in South America. The Guterman colorimetric test [19, 20] for pregnandiol has not yet been generally accepted and is still the subject of some difference of opinion.[21]

The test for total neutral *17-ketosteroids* [43] is probably the next most widely performed. It gives a colorimetric end-point and has become accepted as an index though not a true measure of androgen activity in the individual. The biological test using capons is still being used in some centers, and of course, remains the true test for androgens.

The *follicle-stimulating pituitary gonadotropins* (FSH) are now being more generally measured, with the method using mouse units [4] the most widely accepted procedure.

Tests for pregnandiol [19, 38] are being carried out in many centers, especially where there is much work in obstetrics and gynecology. It will be recalled that pregnandiol is principally the excretion product of progesterone.

The fluorometric test for estrogens [35, 36] while not yet in wide use, shows promise of being a relatively simple method.

Glycogenic corticoids from the adrenals have been measured extensively clinically but not in many centers. It will be recalled that this is a biological test which requires adrenalectomized mice.[27] The colorimetric test for 11-

oxycorticosteroids [30] has also had clinical trial but in a limited number of centers. Elevation of values seems most marked in Cushing's syndrome and they are reported to drop to normal levels if the disease becomes inactive.

Experience at the University of California Medical School

Tests for 17-ketosteroids and for follicle-stimulating hormone have been available at the University of California Hospital for the past three and a half years.* The Hormone Laboratory was set up and organized by Doctor Nellie Halliday, and started to function in September, 1944. At first only tests for 17-ketosteroids were available but soon the bioassay for FSH was set up. Dr. Halliday supervised the laboratory and trained all technical help until December, 1946. Since then, the tests for 17-ketosteroids have been run in the laboratory of Dr. Gerson Biskind and tests for FSH have been performed in the Endocrine Laboratory of the Department of Obstetrics and Gynecology under the supervision of Dr. Allan Palmer.

Methods—17-Ketosteroids

Under Dr. Halliday the urines were extracted by the method of Pincus [66] using the Zimmermann reaction which is summarized in table 2.[66, 67] The separation was carried to the ketonic fraction which, it will be remembered, represents 85 to 90 per cent of the total neutral 17-ketosteroids in fairly constant proportion.† The colorimetric estimation of end-points was performed according to the method of Holtorff and Koch [68] using the Klett-Summerson photoelectric colorimeter connected through a G–E voltage stabilizer. It is of interest that Nathanson and Wilson [55] compared several methods of colorimetric estimation and preferred this one because of less technical difficulty and smaller error.

In Dr. Halliday's experience, the normal ranges were as follows:

Women over 16 years (36 cases): 5.5 to 11.4 mg. per 24 hours Ketonic, with an average of 8.7 mg. ± 1.6 mg.
Men over 16 years (16 cases): 10.7 to 20.6 mg. per 24 hours Ketonic, with an average of 14.7 mg. ± 3.0 mg.

The convenient fraction of 10 per cent was added to these figures in order to make them comparable with the figures of other authors whose results are reported as the total neutral fraction. This comparison with normal ranges noted by several other authors is made in table 3.

* The laboratory was started under the leadership of Dr. H. Lisser with the assistance of Dr. Evelyn Anderson, Department of Medicine; Dr. Francis S. Smyth and Dr. William C. Deamer, Department of Pediatrics; and Dr. Robert A. Lyon, Department of Obstetrics and Gynecology. The organization and maintenance were aided by generous contributions from the Ciba Pharmaceutical Company and from the Christine Breon Fund for Medical Research as granted by the Research Committee under the chairmanship of Dr. Theodore L. Althausen.

† However, in some instances, Dr. Halliday found the non-ketonic fraction to comprise as much as 25 per cent of the total.

TABLE II

Flow Chart for Extraction of 17-Ketosteroids from Urine

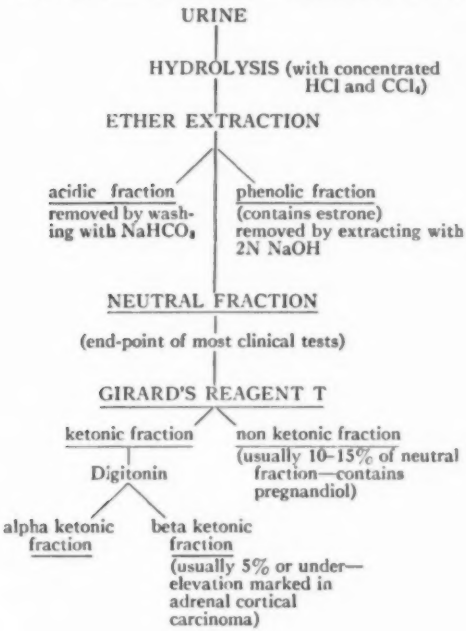


TABLE III

Comparison of Normal Values for Total Neutral 17-Ketosteroids as Mg. per 24 Hrs. from Different Laboratories

Author	Females			Males		
	Lower	Upper	Average	Lower	Upper	Average
Univ. of Calif., Dr. N. Halliday	6.0 mg.	12.5 mg.	9.6±1.8 mg.	11.8 mg.	22.7 mg.	15.2±3.3 mg.
Callow et al., 1939[46]	1.7 mg.	12.6 mg.	6.75 mg.	3.5 mg.	15.0 mg.	9.05 mg.
Fraser et al., 1941[43]	5.1 mg.	14.2 mg.	9.0 mg.	8.1 mg.	22.6 mg.	13.8 mg.
Talbot et al., 1943[69]	2.8 mg.	9.2 mg.	6.8 mg.	8.8 mg.	15.6 mg.	11.0 mg.
Luft, 1943[78] (from Sweden)	12.4 mg.	23.1 mg.		14.3 mg.	43.1 mg.	
Hoffman, 1944[70]	5 mg.	18 mg.	10 mg.	7 mg.	27 mg.	15 mg.
Venning and Browne, 1947[28]	7 mg.	18 mg.	11 mg.	10 mg.	25 mg.	17 mg.
Forbes et al., 1947[48]	3.8 mg.	16.9 mg.	8.2 mg.	6.7 mg.	27.2 mg.	12.5 mg.

Ranges for children (boys and girls) were taken from Talbot et al.[60] and were as follows:

Up to 3 years—none.
At 8 years—0 to 2.0 mg. per 24 hours total neutral, with an average of 0.95 mg.
At 12 years—1.5 to 5.0 mg. per 24 hours total neutral, with an average of 3.4 mg.
At 16 years—4.0 to 9.5 mg. per 24 hours total neutral, with an average of 7.2 mg.

They noted that in general the values approximate 0 under the age of 10, and should be at least 1 mg. by the age of 12. The adrenal cortex was thought to be the chief source of 17-ketosteroids during childhood.

Dr. Biskind used a method slightly modified from that of Robbie and Gibson [58] and reported values as total neutral 17-ketosteroids. He did not proceed beyond this step to separation of the ketonic fraction.

In appraising the results expressed below, the normal diurnal variation must also be considered. It was reported by Werner [59] that daily total neutral 17-ketosteroids fluctuated from 6 mg. to 14.2 mg. and from 10.1 to 17.3 mg. in two normal males, while in one female the fluctuation was from 6.9 to 12.2 mg. per 24 hours. However, Forbes and co-workers [45] in 1947 felt that although there was wide variation in the normal range, repeated estimations on the same individual showed considerable consistency. They also noted that after any medical or surgical injury, the excretion would rise for one to three days and then fall to below the usual normal level—returning gradually to normal as convalescence was achieved. Dingemanse et al.[63] reported from Holland that the 17-ketosteroid excretion was higher in post-war normal urine specimens than in those collected during the war, and suggested that the inadequate or unbalanced diet that prevailed for many years there during occupation had been a factor in depressing the values.

The FSH method used by Dr. Halliday was a slight modification of the test of Klinefelter, Albright and Griswold [4] which has been described above in the section on "Tests Now Used." The chief modification was the difference in adjustment of volumes so that several levels could be tested on the same urine specimen. She found normal patients to be in the following ranges:

Adult men and women (non-menopausal) 6 to 50 mouse units per 24 hours.
Children: very low.

Dr. Palmer also used the method of Klinefelter, Albright and Griswold, considering a positive reaction a 50 per cent or more increase in weight of the uterus. The ovaries were also examined histologically to rule out any possible estrogenic effect in causing the increase in uterine size. In his experience the normal range in adult men and women (non-menopausal) varied from 5 to 40 mouse units per 24 hours.

Results

Four hundred and eighty-eight estimations of 17-ketosteroids and 233 estimations of FSH are available for this report.* The results are listed under diagnoses.

In all instances 10 per cent was added to the figures for ketonic fraction in order to make them comparable with those for the total neutral fractions. This convenient percentage seems permissible considering the variations in the test, in the daily output, and in the range of normal values.

Acromegaly

17-Ketosteroids were estimated in 14 cases. The 24-hour value for total neutral fraction varied from 4.9 mg. (in a female patient aged 60 with diabetes) to 25.5 mg. (in a male patient aged 58 with clinical evidence of moderate activity). The average value of the five male patients was 23.4 mg. per 24 hours and of nine female patients, 11.2 mg. per 24 hours. Thus the male patients were slightly high, being on the average above the normal range, and the female patients were generally higher than average, but within the range of normal.

Fraser et al.[43] in 1941 reported one male patient with a level slightly below the normal range and five females, three with levels below normal and two with levels in the upper limits of normal. In 1943 Klinefelter et al.[4] reported on three males—one was under normal, one was low average and one slightly over normal. There were also seven female acromegalics, of whom three showed slightly low levels (the lowest having diabetes), three normal levels and one slightly high. Hoffman in 1944[70] reported on six patients, three of whom were low and three normal. In 1947 Venning and Browne[28] reported two males with values slightly above normal and two females with levels within the upper limits of normal.

FSH was determined nine times in eight patients. The excretion was within normal range in six patients, definitely above normal in one, and at least normal in another. Of the last two, one patient was a female, aged 34 whose urine showed a positive test for 94 mouse units per 24 hours and a negative test for 140 mouse units. The other case was in a male of 24 with active acromegaly who showed a positive test at 30 mouse units, which was the highest level tested.

Klinefelter et al.[4] in 1943 reported on FSH in acromegalics. Seven were low, two normal and one was high. The latter was a female aged 40 who had passed the menopause.

* Patients tested have been from all departments of the University of California Hospital and Clinic and comprise both private and clinic cases, including those of Dr. Leela S. Craig, Dr. L. E. Curtis, Dr. W. C. Deamer, Dr. M. B. Goldberg, Dr. G. S. Gordan, Dr. L. W. Kinsell, Dr. H. Lisser and Dr. R. Perlman. The data are available as a result of the team work and generosity of all the above. Future publications by members of this group will undoubtedly present some of the work in greater detail.

Simmonds' Disease

Nine patients with this diagnosis were tested 14 times for 17-ketosteroid output. One instance was in a boy aged 12 who also had diabetes insipidus. His level was 3.2 mg. total per 24 hours. The rest were adults of whom four were males and four were females. The ranges in the males varied from 1.1 mg. to 4.7 mg. per 24 hours with an average of 2.7 mg. total neutral per 24 hours.

In the four female patients, the variation was between 1.8 mg. and 4.0 mg. with an average of 2.7 mg. total neutral per 24 hours.

Thus in the younger patient, the value was within normal limits, but below the average, while in the adults the values were below the normal range in all cases, with the averages of sexes equal, and therefore being especially low for the male patients.

This differs with some of the earlier reports in the literature. Fraser et al.[43] in 1941 reported nine cases with values in eight being under 0.5 mg. per 24 hours. Hoffman [70] in 1944 reported 15 patients, with only one showing an excretion of over 1 mg. Klinefelter et al.[4] in 1943 also reported very low values, mostly under 0.5 mg. Slightly higher values were reported by Talbot et al.[80] in 1947 with levels of 1.4 and 1.6 mg. in two patients, and Venning and Browne in 1947 [28] reported five adults with values up to 3.5 and 4.2 mg. though all were definitely below the normal range.

FSH was tested 15 times in eight patients. In the patient mentioned above (a boy aged 12), the test was positive at 4 mouse units and negative at 11 mouse units per 24 hours. Of the remainder, negative tests were reported at 7.2, 9.0, 6.7, 6.4, 3.0, 2.9, 5.5, 2.8, 7.1 and 3.2 mouse units per 24 hours, indicating that the patient's output was under these levels. However, positive tests were reported at 8.0, 3.8, 20, and 8.1 mouse units per 24 hours. The high level was in a patient where two previous tests had shown (1) positive results at 8 mouse units and negative at 23 mouse units, and (2) negative at 7.2 mouse units per 24 hours. She had had diabetes before the onset of her disease which followed a pregnancy and had then developed the Houssay phenomenon with marked amelioration of the severity of the diabetes and extreme sensitivity to insulin.

Klinefelter, et al.[4] in 1943 reported low levels in 10 cases. Two had positive tests at 3 mouse units and negative tests at 6.6 mouse units. One doubtful case was positive at 6.6 mouse units. All the rest were negative at levels of 3 and 6.6 mouse units per 24 hours.

Anorexia Nervosa

17-Ketosteroids were measured 16 times in 12 patients with this diagnosis. All were adults and all but one were in females. The only male, a man of 49, showed a level of 1.8 mg. total per 24 hours—lower than any of the male patients in this series with true Simmonds' disease. The 11 female patients varied from 1.5 mg. to 14.8 mg. with an average of 7.3 mg. total neutral per 24 hours. Thus although the average of these patients was

within the normal range, it must be pointed out that there is overlapping with the values found in the patients with Simmonds' disease. Individual values of 1.8, 2.1 and 1.5 mg. per 24 hours in anorexia nervosa are lower than those of 3.1, 2.2, 4.7, 3.9 and 3.2 which were found in the patients with Simmonds' disease and indicated that, in our experience, the test is not always helpful in deciding whether an individual case is one of anorexia nervosa or Simmonds' disease.

Fraser et al.[48] in 1941 reported mostly low normal values, but levels as low as 1.7, 2.4, and 3.6 mg. were included. Klinefelter et al.[4] in 1943 reported a similar spread in five patients with low values such as 1.2, 1.8 and 1.9 being included. In 1947 Venning and Browne [28] reported low (3.5 to 4.0 mg.) and low normal figures in three patients, and Sunderman and Rose [71] in 1948 reported a patient, a female of 28, with a value of 2.3 mg. per 24 hours for 17-ketosteroid excretion. Landau, et al.[72] in 1948 reported that 17-ketosteroid excretion was cut in half by four days of starvation.

FSH was tested in eight patients a total of 10 times, all of whom were adult females. Four showed negative results at levels of 8.5, 8.0, 4.2 and 48.6 mouse units per 24 hours. Positive results were reported at 17.9, 45, 6.7, and 5 mouse units per 24 hours. Two patients showed doubtful positive results (one animal positive and one negative) at levels of 32 and 136 mouse units per 24 hours. Thus most were within normal range. In one patient, a typical instance in a female aged 27, three urine specimens were reported as showing the following values:

1. Positive at 6.7, negative at 40.2, m.u./24 hours.
2. negative at 4.2, m.u./24 hours.
3. Plus-minus at 32, m.u./24 hours.

showing how the results of the test can vary in the same patient.

Klinefelter et al.[4] in 1943 reported normal values in five patients while Sunderman and Rose in 1948[71] reported an FSH of 0. in their patient.

Hypophyseal Infantilism

17-Ketosteroids were determined 25 times in 22 cases with this diagnosis. One patient, a boy aged four and one-half, was within normal range for his age with a value of 1.6 mg. per 24 hours.

Six patients aged 8 to 11 ranged in excretion from 0.6 to 11.9 mg. with an average of 3.9 mg. per 24 hours. This is slightly above the normal average for that age. The patient with the high level was a girl aged nine with a craniopharyngioma.

In the group from 12 to 15 years, there were seven patients. Values ranged from 1.0 to 6.2 mg. total neutral, with an average of 4.0 mg. per 24 hours. This was at the lower limit of the normal range, and definitely below the normal average.

Males of adult age in this group numbered six and their values ranged from 1.2 to 5.9 mg. with an average of 3.5 mg. total neutral per 24 hours. This is, of course, well below the normal range.

Two adult females showed values of 0.7 mg. and 1.1 mg. with an average of 0.9 mg. per 24 hours.

Thus in our experience with patients with hypophyseal infantilism, the 17-ketosteroids were normal until the age of 12, low normal up to 16, and definitely below normal once adult age has been reached, especially in females.

In 1941, Fraser et al.[43] reported seven patients, all with values under 0.5 mg. Then in 1943, Klinefelter, et al.[4] reported five patients, all low, with three showing values under 0.5 mg. Talbot et al.[69] reported nine cases with an average age of twelve and one-fourth years—all with low levels. Engstrom and Mason [73] in 1944 reported a boy of 18 with low levels (0.4 to 0.8 mg. per 24 hours). In 1947, Talbot et al.[30] reported three adults with low levels, but Venning and Browne [28] reported a girl of two and one-half with a slightly high level (3.2 mg. per 24 hours).

FSH—21 estimations were reported on 18 patients. *Negative* tests for patients under 16 years of age were obtained at levels of 3.7, 12.8, 6.0, 10.1, and 4.8 mouse units per 24 hours. These were the lowest levels tested in these cases. *Positive* results in patients in this age group were reported at 4.2, 3.9, 3.0, 24.6, 8.0 and 5.0 mouse units per 24 hours and *doubtful positive* tests at 34, 8.2, and 33.6 mouse units per 24 hours (one animal positive, the other negative). Of the six patients of adult age, four showed negative values at (1) 7.3 and 5.2; (2) 6.4; (3) 6.4, and (4) 11.6 mouse units per 24 hours, lowest levels tested, and two patients had positive values at 5.9 and 8.7 mouse units per 24 hours.

From this, one must conclude that the FSH in hypophyseal infantilism is usually within normal range, though most frequently in the lower levels. Occasionally it is below normal levels.

Klinefelter et al.[4] in 1943 reported low levels in five patients.

Pituitary Malfunction or Hypopituitarism

Eleven tests were run for 17-ketosteroids on 11 patients so labelled. Six were in the age group, 12 to 15, and showed values ranging from 1.2 mg. to 16.4 mg. with an average of 7.1 mg. total neutral per 24 hours. The highest level was in a boy aged 14 who had diabetes insipidus.

One male adult was in the series and showed a level of 18.1 mg. total per 24 hours. He was a man of 58 who had scant sexual hair and atrophic testes.

The four adult female patients ranged from 4.3 mg. to 8.4 mg. with an average of 6.9 mg. total neutral per 24 hours—slightly below the normal average.

Fraser et al.[43] in 1941 reported two patients with pituitary tumors. The level of excretion in one was low, and in the other, it was normal. Talbot et al.[30] and Venning and Browne [28] each reported patients with pituitary tumors who showed slightly low levels of 17-ketosteroids.

FSH tests in this group totalled five. One in a boy 15 years of age was under 6.7 mouse units per 24 hours. The other four in adult females were within normal limits. One interesting patient, a woman of 35, had developed a carcinoma of the nasopharynx 11 years before. Following operation, she had been given heavy roentgen therapy to the area, and it is estimated that approximately 4000 r reached the pituitary region. Following this, the patient developed the following symptoms of hypopituitarism: Loss of weight and then inability to gain, severe exhaustion, marked atrophy of breasts, diminution of libido, inability to conceive (two previous normal pregnancies) and change in menstrual function from a regular 28-day cycle with periods of moderate flow lasting three to four days, to an irregular cycle with intervals of one to four months and very scant periods lasting one-half to one day. To the author's surprise, FSH level in this patient was positive at 30 mouse units per 24 hours. Repeat tests were (1) positive at 5 m.u. and negative at 80 m.u.; (2) positive at 15 m.u. and negative at 30 m.u. It is difficult to reconcile these results with the clinical picture.

Hyperthyroidism

17-Ketosteroids were tested seven times in six patients. Two males showed values of 77.3 and 9.7 mg. total neutral, and four females had values of 11.8, 9.2, 8.2, 7.6 and 8.5 mg. total neutral per 24 hours. All were therefore within normal limits except the one male patient with the high level of 77.3 mg. He was reported as having a BMR of + 37 per cent and showing no other reason for the high ketosteroid excretion.

Baumann and Metzger [40] in 1940 reported normal or slightly low levels in five patients and Fraser et al.[42] in 1941 reported low levels in three patients. Engstrom and Mason [73] collected 22 patients with hyperthyroidism and found the values in all to be slightly low. Forbes et al.[45] in 1947 reported on 19 patients, all with slightly low levels. Venning and Browne [28] that same year reported a case with a low normal level.

FSH was measured five times in four patients. All were adults and showed the following values:

Male, age 56—positive at 43 mouse units/24 hours.
Male, age 41—positive at 6.9 and negative 51.2 mouse units/24 hours.
Female, age 40—± at 64 and negative at 132 mouse units/24 hours.
—positive at 60 and negative at 128 mouse units/24 hours.
Female, age 26—positive at 7.4 and negative at 44.1 mouse units/24 hours.

It can be seen that one patient tended to be slightly high, two were within normal limits and one had a level that was at least normal.

Hypothyroidism

17-Ketosteroids were measured once each in 10 patients. Three male patients showed values of 25 mg., 16.4 mg. and 4.8 mg. total neutral per

24 hours. The last case was one of severe myxedema as yet untreated in a man of 67. Seven female patients showed values ranging from 4.2 mg. to 22.9 mg. with an average of 13 mg. total neutral per 24 hours. These figures somewhat exceeded the usual normal range, and in females, therefore, the average was slightly high.

Values have been reported lower than this in the literature. Baumann and Metzger [60] in 1940 reported a value of 3.6 mg. in a female patient aged 40 with myxedema. Fraser et al.[43] in 1941 reported levels as low as 1 mg. or under 0.5 mg. with all values being definitely low. Talbot et al.[69] in 1943 reported low values in 12 children and in 1944, Engstrom and Mason reported [73] low values in 10 patients. Benda and Bixby [74] in 1947 reported low values in three adult cretins and in one hypothyroid.

FSH was tested five times in as many cases. The only male was the case of severe myxedema already mentioned and his report was of a positive test at 30 mouse units per 24 hours, so his level was at least that high. The four female patients were all within normal range.

Klinefelter et al.[4] in 1943 reported a normal FSH in one patient.

Diabetes Mellitus

17-Ketosteroids were tested six times in as many patients. One male showed a level of 1.2 mg. per 24 hours. This specimen was collected after an operation for removal of a thyroid nodule. The five female patients were all adults. Three were definitely hirsute and showed levels of 4.7 mg., 13.3 mg. and 9.5 mg. One was a patient with ovarian aplasia and showed a level of 5.2 mg. The last patient, a girl of 16, excreted 6.2 mg. total neutral per 24 hours. Two of these female patients were, therefore, below the usual normal range; but none were above the normal range, even the bearded diabetics.

Fraser et al.[43] in 1941 reported results in four females and two males with diabetes. All but one were slightly below the normal range and that one was below the average normal. Miller and Mason [75] in 1945 studied the excretion in 64 adults and 17 juvenile diabetics. All were below average normal and most were below the normal range. They found no correlation with the severity of the diabetes. In 1946 Salter et al.[61] reported low levels in two patients, though the diabetes was complicated in one case by eunuchoidism, and in the other by Addison's disease. Venning and Browne [28, 29] in 1947 reported four cases in whom the 17-ketosteroid output was normal. That same year, Forbes et al.[45] reported nine females with low outputs, the average being 5.1 mg. and six males with an average output that was even lower at 4.6 mg.

FSH was measured in only two cases, with negative results. One in a boy of three was negative at a level of 3.2 mouse units per 24 hours and the other in a girl of 19 was negative at 7.9 mouse units per 24 hours. The latter patient had been a severe juvenile diabetic, was rather short, and was still amenorrheic at that age.

Cushing's Syndrome

17-Ketosteroids were tested 13 times in 11 patients. One was a girl aged 11 whose excretion level was 4 mg. total neutral per 24 hours. Two male adult patients excreted 29.3 mg. and 12 mg. per 24 hours respectively, and in eight females the values ranged from 5.6 mg. to 20.3 mg. with an average of 16.6 mg. total neutral per 24 hours. While this is above the usual normal range, the elevation is not marked.

Fraser et al.[43] in 1941 reported slightly elevated levels in four patients, one with adrenal carcinoma. Another case with adrenal carcinoma was high with an excreted level of 74 mg. per 24 hours. Hoffman[70] in 1944 reported that in cases without adrenal cortical carcinoma the values were normal or slightly high (range 7.5 to 36 mg. per 24 hours), but in five patients with adrenal carcinoma the values were high (range 40 to 288 mg. per 24 hours). Salter et al.[61] in 1946 reported moderately high values in a girl of 12 years (12 mg.) and found the proportion of alpha and beta partitions to be normal. In 1947 Talbot et al.[30] reported eight patients. Two were slightly low, one was normal, three were slightly above the normal range and two were moderately elevated (44 and 51 mg.). Venning and Browne[28, 29] reported seven cases, of which four were normal and three slightly high. Kepler and Mason[76] reported three cases—one was normal and two were slightly high (24 and 28 mg.). Beta fractions were also measured and were 2 per cent and 5 per cent in two of the cases, but in the third patient, a woman aged 27 whose total excretion was 24 mg., the beta fraction was 14 per cent.

FSH was tested four times in a like number of patients. All were adults and two were within normal limits. The other two showed higher levels. One, a female of 38, was positive at 51.2 mouse units per 24 hours and doubtfully positive at 96 mouse units. Another female patient of 27 showed a positive reaction at 51 mouse units, but no higher levels were tested.

Adrenogenital Syndrome

(Hyperadrenalism, Pseudohermaphroditism)

17-Ketosteroids were estimated 55 times in this group of 48 patients. Two female patients had carcinoma of the adrenal. One, a female, fifteen and a half years old, did not have an elevated level, excreting 6.8 mg. total neutral per 24 hours. The other showed a pre-operative level of 82.1 mg. total neutral per 24 hours and after operation, the output dropped to 6.3 mg. In seven months the level had increased to 19.3 mg. per 24 hours, indicating a possible but not proved recurrence of the tumor. Additional evidence for this conclusion was furnished by the fact that the beta fraction in this patient was 55 per cent pre-operatively, and post-operatively was still at 29 per cent. It will be recalled that the beta fraction is usually under 5 per cent and seems to increase particularly with adrenal cortical carcinoma. The analyses for this fraction were kindly performed for us by Dr. Ralph I. Dorfman.

Seven patients were in the age range three weeks to two years, where

normally no 17-ketosteroids are detected. Eight values were done and ranged from 0.4 mg. to 17.5 mg. with an average of 7.6 mg. total neutral per 24 hours.

In the age group three to seven, there were 13 patients and levels of excretion ranged from 1 mg. to 15.4 mg. with an average of 4.5 mg. total neutral per 24 hours. The highest level was in a boy aged three with the adrenogenital syndrome.

Patients between the ages of eight and 11 numbered 12 and each had one test. The values varied from 2 mg. to 11 mg. with an average of 4.9 mg. total neutral per 24 hours. The highest was in a male aged nine with precocious puberty.

In the group between 12 and 15, there were four patients. Values were 7.1 mg., 8.2 mg., 8.7 mg., and 75.6 mg. total neutral per 24 hours. The latter case was a girl of 12 who had had two previous operations on the adrenals but was still hirsute, with masculine build. At the first operation, half of the left adrenal had been removed and had shown marked hyperplasia, also an adenoma had been removed from the cortex of the right adrenal. Four years later (at the age of nine) the remainder of the left adrenal had been removed and still showed marked hyperplasia.

Only two adult "male" patients were in this group. Both were pseudohermaphrodites. One showed values of 22.7 and 23.1 mg. per 24 hours, but the other aged 24 excreted 166.6 mg. total neutral per 24 hours. This remarkable individual had a short muscular, very masculine body configuration with apparent hypospadius and undescended testes. On exploration, however, ovaries were found. There was no evidence of adrenal tumor.

The remaining eight cases were all adult females and showed values ranging from 10.1 mg. to 95.5 mg. with an average of 28.5 mg. total neutral per 24 hours. The patient with the high level was another instance of adrenal cortical hyperplasia in a girl of 16 in whom one adrenal and a third of the other had been previously removed.*

There are numerous reports in the literature of patients of this type. In 1940 Baumann and Metzger [60] reported one patient with adrenal carcinoma who showed a low level (2.3 mg.) three weeks after operation, but later, after recurrence of the tumor, excreted 367 mg. per 24 hours of which 111 mg. were in the beta fraction. Fraser et al.[43] in 1941 reported three cases— one girl, aged three and one-half, with an adrenal tumor excreted 176 mg.— three with adrenal hyperplasia were moderately increased, with levels up to 72.4 mg. in a woman of 23. Nathanson and Aub [77] in 1943 reported slight elevation (to 3.5 mg.) in a boy of four and one-half years of age with precocious puberty. That same year, Luft [75] reported on two boys. One aged two and one-half with adrenal hyperplasia excreted up to 52.5 mg. The other, aged seven, who

* Since the original preparation of the manuscript, an instance of virilism has been seen in a woman aged 63. Increased beard and body hair growth, baldness, amenorrhea, and an enlarged clitoris had gradually developed over a period of 30 years. 17-Ketosteroid excretion was 741 mg. total neutral per 24 hours with a beta fraction of 170 mg. (23 per cent). A large, encapsulated adrenal cortical carcinoma was removed surgically. One week later, the 17-ketosteroid had dropped to 15.8 mg. and one month later, the level was 9.1 mg. total neutral per 24 hours.

had a carcinoma of the adrenal, excreted 155 mg. per 24 hours. In 1944 Engstrom et al.[79] reported eight patients with adrenal tumor—four were moderately increased (up to 54.6 mg. in a girl of 16) and four were markedly increased with the highest level of excretion being 857 mg. in a woman of 45. They also reported three patients with pseudohermaphroditism and adrenal hyperplasia. All showed definite increases, the highest being 75 mg. in a girl of 19. Hoffman[70] reported eight patients with adrenal carcinoma. Two were adults and showed high levels (215 and 367 mg.) and six were children, all of whom were high, with four being over 100 mg. and the highest level at 420 mg. Twenty-two of his patients had adrenal cortical hyperplasia. Five of these were adults and varied from 35 to 52 mg. and 17 were children, with excretions varying from 17.8 to 74 mg. Raices and co-workers[80] in 1945 reported two patients, one with adrenal tumor and the other with hyperplasia. Both had normal 17-ketosteroids. Warren[81] that same year reported four patients with tumor in whom high levels were found (83, 690, 269, and 126 mg.). Two female children aged seven and ten and one-half with virilism showed an excretion level of 158 mg. during a pregnancy. After delivery the level dropped to 23 mg. and later, after removal of an ovarian tumor, to a still lower level of 12.8 mg. Three weeks after birth, the child, who appeared to be a normal male infant, was found to excrete 138 mg. per 24 hours. A study by Salter et al.[61] in 1946 showed normal, moderately elevated and high levels in a series of 10 patients. The highest excretion was 800 mg. and occurred in a patient with adrenal carcinoma. The beta fraction in this case was 222 mg. Herweg et al.[82] in 1946 reported two patients who were feminized males. In both, the 17-ketosteroid excretion was normal. In 1947 Venning and Browne[28] reported moderate increase of 17-ketosteroid excretion in a boy of two and one-half years of age. Talbot et al.[30] reported moderate elevation in five patients with adrenal cortical hyperplasia, and marked elevation to 830 mg. in one patient with adrenal carcinoma. Kepler and Mason[76] reported six patients with adrenal tumor. One patient showed normal excretion, two others showed moderate increase and the remaining three were high, with the top level being 1005 mg. in a woman of 55. The beta fraction in that patient was 77 per cent. Two patients with hyperplasia showed levels of 31 mg. in a girl aged 10 and 123 mg. in an adult. The beta fractions in these cases were 14 and 20 per cent. These authors concluded that values of over 50 mg. with a beta fraction of over 50 per cent were strong evidence in favor of an adrenal carcinoma. In 1948 Dobriner et al.[67] reported two patients with hyperplasia who showed 17-ketosteroid levels of 62 and 53.7 mg. and whose beta fractions were 5 per cent and 8 per cent. Two other patients had adrenal cortical tumors. One had a high level of 17-ketosteroid excretion (192.8 mg.) and the other showed a moderate increase (71 mg.). The beta fraction, however, was high in both cases—38 and 27 per cent. Wilkins[83] reported two interesting cases. One was a boy, aged 5, with gynecomastia in whom an adrenal tumor was successfully removed. His level of excretion was only slightly increased (4.1 mg.). The other patient was a girl of the same age with virilism due to an adrenal carcinoma. Her level of excretion was 22 mg. before operation. Afterwards it dropped to 0.9 mg. but 11 months later had risen to 126 mg. She was reoperated upon and the level dropped to 16 mg., but three and one-half months later was back up to 124 mg. The beta fraction in this patient was less than 1 per cent.

FSH determinations in this group numbered 14 and 13 patients.

Those in the two cases of marked adrenal cortical hyperplasia briefly mentioned above were as follows:

Female, age 12 (17 KS—75.6 mg.)—positive at 9.5 mouse units and doubtfully positive at 19 mouse units per 24 hours.

Female, age 16 (17 KS—95.5 mg.)—positive at 9.1 mouse units and doubtfully positive at 18.2 mouse units. Negative at 46 mouse units per 24 hours.

Of the remaining 11, 10 showed precocious puberty and one, a female, aged four, was a pseudohermaphrodite. All were under nine years of age. The values in seven were negative for the lowest level test, which varied from 2.8 to 6.6 mouse units per 24 hours. The remaining four showed levels as follows:

Female, age 7—positive, 11.5 m.u.—negative, 23 m.u.
Same patient, age 8—positive, 8.0 m.u.—negative, 12 m.u.
Female, age 8—positive, 3.2 m.u.—negative, 19.2 m.u.
Female, age 5—positive, 3.2 m.u.—negative, 19.2 m.u.
Female, age 8—positive, 4.8 m.u. per 24 hours—highest level tested.

Apparently, a slight increase in FSH is seen in about half of these cases.

Nathanson and Aub[77] in 1943 reported a high level in a boy of four and one-half years with precocious puberty (positive at 120 mouse units). Wilkins[83] in 1948 reported a level of under 6.5 mouse units in the boy with gynecomastia and an adrenal tumor mentioned above.

Hirsutism

This finding in females has been the reason for many of our tests for *17-ketosteroids.* One hundred and thirteen determinations were made in 98 patients. Some of the patients had amenorrhea, some were obese, and one was pregnant, but otherwise there were no apparent endocrine complications. All patients were females and two were young, aged five and six. They both excreted 1.6 mg. per 24 hours—within the normal range for that age.

In the 96 adult females the excretion ranged from 2.3 mg. to 44.2 mg. with an average of 15.2 mg. total neutral per 24 hours. This is somewhat above the normal average of 9.6 mg. and even slightly above our normal range (6 to 12.5 mg.) but the difference is not enough to be of any diagnostic significance. In the patient who was pregnant, the values were 16.1 mg. and 18.1 mg. during the pregnancy and 11.8 mg. after delivery.

The values in some of the patients tended to drop after therapy with estrogens, i.e., from 24.3 mg. to 15.9 mg.—from 12.6 mg. to 10.8 mg.—and from 13.6 mg. to 10.2 mg. However, these figures are not conclusive as they are within the limits of the normal diurnal variations.

Baumann and Metzger[60] in 1940 reported on two patients with simple hirsutism. Both showed slightly high levels but the beta fractions were not elevated. Fraser et al.[43] in 1941 reported on one patient who showed a high normal level of excretion of 17-ketosteroids. Raices et al.[80] in 1945 reported on 75 patients. They found the values to be normal in 26 and high in 49. Of the latter group, 22 were 30 mg. or over. It is of interest that their paper is from Buenos Aires where a higher percentage of the women might be expected to be slightly hirsute. Salter et al.[81] in 1946 reported on eight patients. Four were normal and the rest slightly elevated. In 1947 Venning

and Browne [28] reported four patients with moderate elevations and Talbot et al.[30] reported three patients in whom the excretion levels were normal in one and slightly elevated in the other two.

Studies of *FSH* were made 14 times in 13 patients of this group. Two showed negative tests at 9.1 and 11.3 mouse units, the lowest tested, and eight were definitely within normal limits. One patient showed a possible increase, with a positive test at 51 mouse units and a negative one at 96 mouse units per 24 hours. Two, both of whom had amenorrhea, showed definitely increased levels as follows:

Female, age 24—positive at 96 mouse units
negative at 192 mouse units
Female, age 19—
(1)—positive at 96 mouse units
negative at 192 mouse units
age 20—positive at 125 mouse units
doubtfully positive at 194 mouse units

The majority of the patients therefore were within the normal range. It seems possible that the two patients with the high values might belong in a different category.

Addison's Disease

17-Ketosteroids were measured 16 times in 12 patients. All were adults and seven were males. In the males, the variation was from 1.0 mg. to 9.7 mg. with an average level of 4.2 mg. total neutral per 24 hours. A value of 1.1 mg. was found in a patient aged 31 who was also a eunuch, having had both testes and one kidney removed because of tuberculosis. Another level in this same man was 3.7 mg. Both were taken while he was under treatment with desoxycorticosterone acetate and methyl testosterone linguets.

Excretion in the five female patients varied from 1.5 mg. to 11.2 mg. with an average of 5.6 total neutral per 24 hours.

The high level was in a patient aged 30 who was taking desoxycorticosterone acetate. This drug is not supposed to cause significant change in the level of excretion.

Low levels would be expected in this disease, especially in the female patients. However, in our group, the average in the male patients was the lowest, while that in the woman patients was only slightly below normal range. This difference from expected levels is also found occasionally in the literature as will be noted in the following short survey.

In 1940 Callow et al.[34] reported low levels in seven cases. The next year Fraser et al.[43] reported five female patients with values under 0.5 mg. and three male patients in whom the average levels of excretion were 2.1, 2.6 and 3.5 mg. In 1942 Cuyler et al.[51] reported low levels in two cases and noted that the values were further depressed by treatment with desoxycorticosterone or adrenal cortical extract. Luft [78] in 1943

reported five female patients. The excretion in one was reported as 0, in another it was 2.5 mg., but the remaining three were within normal limits (6.4, 9.8 and 14.8.). In two of these patients the values dropped after the administration of desoxycorticosterone. Hoffman [70] in 1944 reported five females with values of less than 0.5 mg. and three male patients with excretion values of 1.2 to 6.4 mg. Salter et al.[61] in 1946 reported six female patients. One was a child of five and one-half years who showed a level of 0.4 mg. In the five adult females, values were from 1.4 to 8.6 mg. One male patient, aged 22, excreted 8 to 10 mg. per 24 hours, with some increase following desoxycorticosterone acetate. In 1947 Venning and Browne [28] reported three female patients with low levels of 2.5, 4.5 and 1.9 mg. and one male with an excretion of 2.8 mg. Talbot et al.[30] reported three females with excretion levels of 0.8, 1.0 and 2.6 mg. and 11 males in whom the values ranged from 1.9 mg. to 4.4 mg. McCullagh et al.[85] in 1948 reported low levels in 13 males and very low levels in seven females. It has been suggested by some that the higher levels reported above may be due to contaminating chromogens that are not true 17-ketosteroids.

FSH levels were measured in two patients and were within normal limits. The values were as follows:

Female, age 45—positive 5.8 m.u./24 hours
negative 46.2 m.u./24 hours
Female, age 30—positive 3 m.u./24 hours
negative 60 m.u./24 hours

McCullagh et al.[85] in 1948 reported normal levels of FSH excretion in seven male patients but in seven female patients, two were normal while the remaining five were high. All of the latter had associated menopausal symptoms.

Eunuchoidism

Twenty-two estimations of *17-ketosteroid* excretion were made in 15 patients. Only one female patient was in this group, a girl of 15, who showed a level of excretion of 7.6 mg. per 24 hours. This is within normal limits, and slightly above average for her age.

The 15 male patients were from 15 to 35 years of age and their range was from 0.3 to 25.2 mg. with an average of 9.0 mg. total neutral per 24 hours. This is somewhat low, being slightly under the normal range. The lowest level was in a patient of Dr. Kinsell. He has reported him [86] as a "panhypopituitary eunuchoid." FSH levels were also low in this patient.

Reaction to treatment with pregnant mare's serum was measured in one patient. His levels before starting were 13.8 mg. and 9.3 mg. per 24 hours, and after one month of treatment the level was 20.6 mg. per 24 hours.

In 1940 Callow et al.[84] reported on five male eunuchoids. All were normal with three in the lower part of the normal range and two in the higher. Fraser et al.[43] in 1941 reported on 11 males and two females. The males were slightly low in nine instances varying from 2.8 to 6.4 mg. and low normal in two others (8.4 and 8.5 mg.). The two females were near the lower limits of normal (5 and 6 mg.). Hoffman [70] in 1944 reported low, low normal, and normal values in eunuchoidism. Heller and Nelson [87] in 1945 reported five eunuchoid males with values ranging from 0.6 mg. to 6.9 mg. Ten moderately severe eunuchoids had moderately low values. Salter et al.[61]

in 1946 reported three males with values ranging from 7.2 to 17 mg. In one patient the beta fraction was as high as 21 per cent. Wall and Hurxthal[88] reported a male, aged 39, in whom excretion levels of 45 and 25 mg. were found. They believed that this patient's adrenals were over-functioning. McCullagh et al.[85] in 1948 reported values of about half the normal average in six male eunuchoids.

FSH was measured 19 times in 13 patients. Two females were in this group and both were high, as follows:

Female, age 20—positive 192 m.u./24 hours
doubtful positive 288 m.u./24 hours
negative 384 m.u./24 hours
Female, age 41—positive 288 m.u.
positive 524 m.u.
positive 376—negative 565 m.u./24 hours

Of the 11 male patients, two were quite low. The patient of Dr. Kinsell referred to earlier, showed negative tests at levels of 3.5, 4.2 and 4.2 m.u./24 hours.

Another man of 34 with a typical eunuchoid picture showed an excretion level under 6.2 m.u. per 24 hours (negative at that level). Further study revealed that he had a chromophobe pituitary adenoma. These two cases might be better classified as primarily hypopituitary in view of their urine hormone studies, although the clinical picture was more typical of eunuchoidism. Six of the male patients were definitely within normal limits and two others were at least normal with positive tests at 3.6 m.u. and 32.4 m.u. per 24 hours, the highest levels tested. Two patients were definitely high (positive at 200 m.u. and 92 m.u. per 24 hours) and one patient was probably high (positive at 61 m.u. and doubtful positive at 108 m.u.). These last three probably should be classified as hypergonadotropic eunuchoidism, and may belong to the group that has been described by Heller and Nelson.[87]

McCullagh et al.[85] in 1948 reported high values (105 to 318 m.u. per 24 hours) in six male patients.

Hypogonadism

A number of cases with this diagnosis were tested for *17-ketosteroids*. Fourteen patients were in the group and 15 tests were run. Two female patients showed values of 20.3 mg. and 11.8 mg. per 24 hours. Two female castrates were also examined. The first, a girl of eighteen and one-half, showed a level of 6.2 mg. per 24 hours, and in the second, a woman of 30, the value was 3.4 mg. Twelve male patients showed levels of excretion varying from 2.9 mg. to 20 mg. with an average of 10 mg. total neutral per 24 hours. This average was lower than the normal average but within the normal range. It was not quite as low as the average level in the eunuchoids. The highest figure was in a patient who had developed typical hypogonadism following a severe genito-urinary infection.

Callow et al.[84] in 1940 reported normal levels in a female castrate of 16. Fraser et al.[43] in 1941 reported on four female castrates and found all to be within the normal range. They also reported on three male eunuchs in whom the levels were slightly low (3.2 to 4.1 and 7.0 mg.). Eleven male eunuchs were also reported by Callow et al.[84] who found the 17-ketosteroids in all to be normal but below the average. Hoffman [70] in 1944 reported that the excretion in male eunuchs was within the range of normal females. McCullagh et al.[85] in 1948 reported that five male castrates showed levels of about one-half the normal average.

Low normal levels in hypogonadism were reported in three patients by Luft [78] in 1943. Salter et al.[61] in 1946 reported a normal level in a hypogonad boy of 13. In this patient the beta fraction was 14 per cent. Venning and Browne [28] in 1947 reported slightly low levels (6.7 and 4.1 mg.) in one hypogonad male aged 40.

FSH was determined 23 times in as many adult patients with this diagnosis. Five were males with four being within normal limits. The fifth was high with a positive test at 96 mouse units and a negative at 192 mouse units per 24 hours. The patient was a man of 38 who had developed hypogonadism following a testicular infection.

Of the 18 female patients, eight were definitely within normal limits, and seven others were probably normal. Three patients showed definitely high values as follows:

Female, age 35	—positive at 96 m.u.
	doubtfully positive at 192 m.u.
	negative at 288 m.u./24 hours
Female, age 29	—positive at 96 m.u.
	negative at 192 m.u./24 hours
Female, age 18½—	
castrate	positive at 288 m.u./24 hours
	negative at 384 m.u./24 hours

Catchpole et al.[89] in 1942 reported on four castrated men. Three showed normal levels of FSH and one was slightly high. Hamilton et al.[90] in 1945 reported on four males who had been castrated before puberty—two showed high levels and two normal levels. McCullagh et al.[85] in 1948 reported high levels in four eunuchs. Catchpole et al.[89] also reported two hypogonad men, one with normal and one with slightly high levels of excretion. They noted a fall to normal levels with alleviation of flashes after treatment with testosterone propionate, and did not feel that methyl testosterone was as effective in this regard.

Hypospadius—Cryptorchidism

17-Ketosteroids in a boy aged three with hypospadius were 0.8 mg. per 24 hours. In another boy aged 11, with cryptorchidism, the value was 10.3 mg. total neutral per 24 hours, somewhat above the normal range of 1.5 to 5 mg.

FSH was measured in one boy of nine with cryptorchidism, and found to be negative at 4.8 mouse units, apparently within the normal range.

Ovarian Aplasia

In this condition, which has been relatively recently described (congenital aplasia of the ovaries, sexual infantilism, short stature, other congenital abnormalities, and high urinary gonadotropins [91]), the *17-ketosteroids* were estimated 10 times in 10 patients.

One patient, aged twelve and one-half, had a level of 1.4 mg., just below the normal range for her age. Another, aged fifteen and one-half, excreted 7.6 mg. per 24 hours—near the normal average for her age. The remaining eight were of adult age and showed values ranging from 1.6 mg. to 23.6 mg. with an average of 8.6 mg. total neutral per 24 hours. Five of the eight values were within normal range and the average figure was only slightly below the normal.

Fraser et al.[42] reported on 17-ketosteroids in five similar cases. All were of adult age and the average values in all were low, varying from 1.6 to 4.7 mg. per 24 hours.

FSH level is most important in the diagnosis of this condition and the values were all high, when the patients were not being treated with estrogens. Twenty-four tests were performed on 14 patients.

Before treatment the values were all elevated, showing positive tests at levels of 27.2 m.u. in the patient aged twelve and one-half, 288 mouse units in a patient aged fifteen and one-half, and in the patients of adult age, 300, 288, 384, 360, 192, 288, 384, 384, 96, 96, 184, 80 and 165 mouse units per 24 hours.

Reactions to treatment with estrogens were of considerable interest. One patient, a woman of 32, had been positive at 300 mouse units, but after one year of treatment with stilbestrol, the urine was positive at 9.2 mouse units and negative at 28 mouse units—within the normal range. After one month without treatment, the level had risen again to positive at 192 mouse units and negative at 288 mouse units. Another patient who was positive at 288 mouse units before treatment dropped to negative at 4.7 mouse units after estrogenic therapy.

Thus, in diagnosing this condition it is important to have the patients off of estrogens for a time (probably one month) before testing for FSH level. The high level which is so important in diagnosis will not be present if they are on estrogenic therapy.

Congenital Aplasia of the Uterus

One patient with this condition, a girl of 16, was studied. Her *17-ketosteroids* were 6.1 mg. per 24 hours—within normal limits, and her *FSH* excretion was under 10.8 mouse units per 24 hours, probably within normal limits.

Gynecomastia

17-Ketosteroids were run in six male patients with this condition. Two boys of 15 showed values of 14.3 mg. and 9.7 mg. per 24 hours. The re-

maining four patients were adults and varied from 6.8 mg. to 17.6 mg., with an average of 12.3 mg. total neutral per 24 hours. This is close to the normal average.

Fraser et al.[43] in 1941 reported on three patients with gynecomastia. All were slightly low. Nathanson [92] in 1942 reported on 21 males, aged 12 to 16, with some breast enlargement. Most were in the low range of normal.

FSH was also measured in six patients. It was within the normal range in five and possibly high in one, a man of 37, where tests were positive at a level of 60 m.u. and doubtfully positive at a level of 120 m.u. per 24 hours.

Nathanson [92] in 1942 reported on 16 boys, aged 12 to 16, with some breast enlargement. In the excretion of FSH, 13 were normal. In one it was slightly elevated, and in two it was high.

Pregnancy

17-Ketosteroids were measured five times in four patients during pregnancy. The value varied from 10 mg. to 19 mg. with an average of 15.8 mg. total neutral per 24 hours. This is slightly higher than the normal range.

Fraser et al.[43] in 1941 reported on three pregnant women—one was high normal and two were low normal. Values tended to be lower after delivery. Benda and Bixby [74] in 1947 reported high normal levels in two women. Dobriner et al.[67] reported normal levels in one patient.

Amenorrhea

In this group were placed cases with this symptom who did not show enough clinically to be classified under another endocrine diagnosis. Eighteen patients were investigated for *17-ketosteroid* excretion and values varied from 3.6 mg. to 21.2 mg., with an average of 9.9 mg. total neutral per 24 hours. Although this range is somewhat wider than normal, the average is almost exactly normal.

Fraser et al.[43] in 1941 reported on seven such patients. Three showed normal levels, three were slightly low, and one was slightly high. Klinefelter et al.[4] in 1943 reported nine patients. Of these, five showed normal levels and four were slightly low. Salter et al.[81] in 1946 reported low normal levels in a patient with amenorrhea and persistent lactation.

FSH was measured in 10 patients of this group. It was normal in four, and probably normal in two more who showed values of (1) positive at 30 m.u., negative at 100 m.u., and (2) positive at 15 m.u./24 hours, highest level tested. Two other patients were negative at the lowest levels tested—12.8 m.u. and 9.6 m.u.—and the two remaining patients were high with levels as follows:

(1) female age 21—positive 192 m.u., negative 288 m.u.
(2) female age 21—positive 149 m.u., negative 298 m.u./24 hours.

Klinefelter et al.[8] in 1943 reported on 10 women. Three were low and seven were within normal limits, including three patients whose amenorrhea had developed post partum.

Menorrhagia—Dysmenorrhea

17-Ketosteroids were measured in two patients aged 19 and 16 with menorrhagia. One value was normal at 8.2 mg. and the other was slightly low at 4.9 mg. total neutral per 24 hours.

FSH was tested in one girl aged 16 with dysmenorrhea and was found to be normal.

Climacteric

17-Ketosteroids were tested 16 times in 15 patients with suggestive symptoms.

Three were females aged 32, 60 and 63 years, and the values were 11 mg., 5.2 mg., and 7.9 mg. total neutral per 24 hours respectively.

Twelve males showed levels ranging from 6.4 mg. to 31.7 mg., with an average of 13.6 mg. total neutral per 24 hours. This is only slightly below the normal average. Two of the men were elderly, aged 70 and 76, and their excretion levels were both below the normal range (6.7 and 7.4 mg. in the first patient and 6.4 mg. in the second).

Fraser et al.[43] in 1941 reported on three women aged 45, 63 and 60. The first two showed low normal values (6 and 7 mg.) and the third was slightly low (3.8 mg.). Salter et al.[61] in 1946 reported low values (1.6 mg.) in a senile man of 78. Hoffman [70] noted that 17-ketosteroid values were low in extreme old age.

FSH excretion was tested in 24 patients. Twelve were females. Of these, four showed the high levels that are considered typical of this condition (positive at 192 m.u., 132 m.u., 120 m.u. and 120 m.u. per 24 hours). The ages of these patients with the high levels were 48, 52, 44 and 65 years. Four patients aged 43, 33, 43 and 45 years were normal and three more aged 32, 40 and 43 were probably normal with values of (1) positive at 24.6 m.u., doubtful positive at 50 m.u., negative at 96 m.u., (2) positive at 24.8 m.u., doubtful positive at 74.4 m.u., negative at 96 m.u., (3) negative at 50 m.u. One patient aged 33 was negative at 6.2 m.u. per 24 hours. She also had hyperthyroidism with diabetes.

Thus the higher levels in this series occurred only in older women, with younger women having normal levels, even though they showed suggestive symptoms. The absence of high FSH excretion may cast some doubt upon the diagnosis of menopause in the latter group.

Of the 12 male patients, three were high, with positive levels at 80, 96 and 170 m.u./24 hours. Their repective ages were 46, 38 and 46 years. Five were normal (aged 76, 46, 47, 55 and 49 years), and three were probably normal (aged 53, 51 and 50). Their levels were:

(1) doubtful positive at 12.1 m.u., negative at 24.2 m.u.
(2) doubtful positive at 9 m.u., negative at 20 m.u.
(3) negative at 24 m.u./24 hours.

One patient was difficult to interpret, having only a single test at a level of 192 m.u. which was negative.

Thus the high levels were not as frequent in the male patients, and it is probable that the diagnosis of the male climacteric will not be made more certain with any greater frequency by the use of this test.

Gonadal Tumors

17-Ketosteroids were tested in two patients aged 42 and 62 with testicular tumors. The values were 9.6 mg. and 8.5 mg. total neutral per 24 hours, both slightly below the normal range.

FSH was tested in one boy aged 16 with possible recurrence of a chorionepithelioma that had been removed four months before. The excretion was high, with a positive test at 120 m.u. and a negative one at 300 mouse units.

17-Ketosteroids were measured in a female aged 40 with a granulosa cell cell tumor of the ovary. The level of excretion was slightly low at 4.6 mg. per 24 hours.

Salter et al.[61] reported slightly elevated levels in a girl of three and one-half with a granulosa cell tumor of the ovary.

Polycystic Ovaries
(Hyperthecosis)

17-Ketosteroids were tested 11 times in five patients with this condition.

One woman aged 21 with menorrhagia had a normal level of excretion at 10.8 mg. per 24 hours. Two other patients with considerable hirsutism had normal values of 7.7 and 6 mg. per 24 hours. The two remaining patients were also hirsute and had high levels of excretion—both were tested again after operation as follows:

Female aged 18— 23.2 mg. per 24 hours before operation and 18.5 and 20.3 mg. after operation.

Female aged 21—26.5 mg., 16.8 mg. and 22.1 mg. per 24 hours before operation and 16.8 and 21 mg. total neutral per 24 hours after the operation. Thus the values dropped slightly but not significantly.

FSH was tested five times in four of the patients. It was normal in three and elevated (positive at 96 m.u. and negative at 192 m.u.) in the one patient who had menorrhagia.

Pheochromocytoma

17-Ketosteroids were tested in a man of 46 with this condition. The level was slightly low, at 7.9 mg. total neutral per 24 hours.

Oligospermia, Sterility, Loss of Potency

17-Ketosteroids were tested in three men with the above diagnoses. Results were as follows:

(1) Age 34—10.2 mg. per 24 hours
(2) Age 32—17.2 mg. per 24 hours
(3) Age ? —23.8 mg. per 24 hours

Therefore all were normal or only slightly above normal.

Fraser et al.[43] reported normal levels in two patients with functional impotence—McCullagh [85] reported that six patients with oligospermia showed normal levels of excretion.

FSH was estimated in one patient with oligospermia and in two male patients who were sterile. It was normal in two and possibly increased in one of the latter (values positive at 51 m.u. and negative at 96 m.u. per 24 hours).

McCullagh et al.[85] reported that his six patients with oligospermia showed high FSH levels (105 to 480 m.u.).

Obesity

17-Ketosteroids were measured in eight cases. Three between the ages of 10 and 15 showed excretion of 3.7 mg., 8.4 mg., and 8.7 mg. total neutral per 24 hours—all within normal limits. Of the five adults, four were females and showed the following levels of excretion—11.9 mg., 11 mg., 5.6 mg. and 14.1 mg. total neutral per 24 hours. The one man aged 40, who was very obese, showed moderate hypogonadism and had hyperostosis frontalis interna. His level was normal at 14.1 mg. per 24 hours. Thus all were within or near the normal range.

Talbot et al.[69] in 1943 reported on nine obese children in whom the average of 17-ketosteroid excretion was normal. Another group of seven very obese children showed slight elevation of the 17-ketosteroids. Nathanson and Aub [77] reported on nine children aged 10 to 16 with adiposogenital dystrophy. In all, the 17-ketosteroids showed excretion that was normal or slightly elevated. Salter et al.[91] in 1946 reported that a male patient of 26 with obesity and gigantism showed a slightly low level of ketosteroid excretion.

FSH was run in two instances, but with negative results. The man aged 40 just mentioned above had a single negative result at a level of 30 m.u. and a very obese girl of 15 had a single negative test at a level of 100 m.u. per 24 hours.

Nathanson and Aub [77] reported normal FSH excretion in eight patients aged 10 to 16 with adiposogenital dystrophy.

Alopecia

Six patients with this condition in varying degrees were tested for level of *17-ketosteroid* output. One girl of fourteen and one-half excreted 6.2

mg. per 24 hours—a normal amount. Three adult females showed values of 20.8 mg., 17.3 mg., and 4.8 mg. total neutral per 24 hours, the figures being both slightly higher and slightly lower than the normal range. Two male patients also showed high normal and slightly low values—17.8 mg. and 6.8 mg. per 24 hours.

Salter et al.[61] reported normal values in a male of 18 with alopecia.

FSH was measured in four of these cases and all were within the normal range.

Fever, Asthma, Arthritis

17-Ketosteroids in three patients with fever, all adult females, were slightly low in two. The values were 3.8 mg., 4.5 mg., and 8.0 mg. One patient with asthma, a male aged 30, was low, with a level of 4 mg. per 24 hours, and one female patient with arthritis aged 29 was within the lower ranges of normal with a level of 6.5 mg./24 hours.

Fraser et al.[63] reported low levels in two patients with arthritis. Davison, Koets and Kuzell [93] studied 13 male patients with Marie-Strumpel type of arthritis and found moderate elevation of 17-ketosteroid output with levels varying from 19.2 mg. to 43.7 mg. with an average of 27.3 mg. Eleven females with rheumatoid arthritis varied from 3.5 to 21.6 mg. with an average of 12.8 mg. This is slightly above the normal average, but within the normal range. Forbes et al.[45] in 1947 studied the output in chronic disease and found it to be generally moderately decreased. A group of 82 male patients with an average age of 44 showed an average output of 6.2 mg., and 114 females of an average age of 37 showed an average output of 4.4 mg.

Miscellaneous

17-Ketosteroids were tested in individual cases of the following conditions:

Osteoporosis. Female aged 56—15.3 mg. per 24 hours.
Congenital Lipodystrophy. Female aged 26—23.9 mg. per 24 hours.
Myotonia Atrophica. Male aged 42—9.0 mg. per 24 hours.
Epilepsy. Male aged 34—14.6 mg. per 24 hours. After one shock treatment the value was 16.6 mg. and after 10 shock treatments the level was 21.3 mg per 24 hours.

Fraser et al.[63] reported two women with osteoporosis. One aged 63 had a low normal level of 6 mg., and the other aged 60 showed a slightly low level of 3.8 mg. They also reported on two women with myasthenia gravis. One was normal at 8.5 mg. and the other slightly low at 4.3 mg. Benda and Bixby [74] in 1947 reported five males and one female with myotonia dystrophica. All were moderately low, the male patients excreting from 4.8 to 8 mg., and the one female showing a level of 2.8 mg. per 24 hours.

FSH was tested in one case of von Gierke's disease in a male aged 18 and showed normal levels.

The following results are from some studies made at the Langley Porter Clinic under Dr. Karl M. Bowman, Dr. A. Simon and Dr. N. Halliday and are included with their permission. They represent a small sampling of an extensive problem, the results of which are now in press in the *Journal of Nervous and Mental Disease.*

Homosexuals

17-Ketosteroids were tested in five patients and all were normal, though in the higher ranges. Three male adults showed values of 12.3 mg., 18 mg. and 17.9 mg. Two females excreted 13.7 mg. and 14.2 mg. total per 24 hours.

Benda and Bixby [74] reported on eight male and two female homosexual patients. The 17-ketosteroids in the males were normal in five and slightly low in three. The two females showed normal ranges of excretion.

FSH was tested in two of these patients, both of whom were transvestites. The male patient (dressed as a female) showed normal levels, but the female aged 25 had a high excretion with a positive test at a level of 192 mouse units per 24 hours.

Manic Depressive Psychosis

17-Ketosteroids were measured six times in two patients. The one male patient showed levels of 13.4 mg., 16.6 mg. and 16.2 mg. total neutral per 24 hours and the female excreted 11.7 mg., 9.9 mg. and 13.2 mg. per 24 hours. These were all within or close to the normal range.

Involutional Depression

17-Ketosteroids were measured three times in two male patients. The values were 14.2 mg., 24.1 mg. and 21 mg. per 24 hours.

Schizophrenia

Twenty-three measurements of *17-ketosteroids* were made in 11 patients. Nine were males, and showed levels varying from 5.2 mg. to 20.5 mg. with an average of 12.9 mg. total neutral per 24 hours. Two female patients were in the group—one aged 26 excreted 15.4 mg. per 24 hours on two occasions. The other aged 17 had amenorrhea and showed levels of 10.2 mg., 10.7 mg., 15.9 mg. and 14.7 mg. per 24 hours. After therapy, this patient showed levels of 11.5 and 14.8 mg. Thus values were normal in the males, and tended to be slightly high in the females.

Anxiety Neurosis

17-Ketosteroids were tested eight times in five patients with this diagnosis. In two males the values were normal, being 12.8 and 12.6 mg.

In three females, the range was from 10.1 mg. to 18.6 mg. per 24 hours, with an average of 15.9 mg.

Thus again the males were within normal limits, and the females tended to be slightly high.

Summary and Conclusions

The availability of a chemical test for measuring 17-ketosteroids in the urine has stimulated more general interest and research in this field of urinary hormonal assays. A review of tests now being used reveals that most are biological assays requiring the use of animals. Outlines of the methods used in most of the tests are given.

Tests more generally available at this time are: those for detecting pregnancy and those for measurement of 17-ketosteroids, follicle-stimulating pituitary gonadotropin, and pregnandiol. Tests for measuring estrogens and the glycogenic adrenal corticoids give promise of more widespread clinical acceptance.

Experience with 488 tests for 17-ketosteroids and 233 tests for FSH at the University of California Hospital has been reviewed. Normal ranges from our experience were compared with those of other authors.

Low values for 17-ketosteroids were found in the following conditions: Hypophyseal infantilism, Simmonds' disease, anorexia nervosa, Addison's disease, myxedema and severe asthma. The average for Simmonds' disease was lower than that for anorexia nervosa, but there was overlapping in the ranges of the two.

High levels of 17-ketosteroid excretion were found in adrenal cortical carcinoma and hyperplasia. When further separation into alpha and beta fractions of the 17-ketosteroids was done, the beta fraction was particularly elevated in the patients with carcinoma. However, one patient with adrenal cortical carcinoma showed normal values.

Slightly high levels of 17-ketosteroids were found in patients with simple hirsutism, Cushing's syndrome, acromegaly, pregnancy and hyperthecosis.

Slightly low levels of 17-ketosteroids were noted in eunuchoidism, male and female castrates, diabetes mellitus, occasionally in the male or female climacteric, and in chronic debilitating diseases. There was a tendency toward lower levels in old age.

The slightly high and slightly low levels are of limited clinical value because of the considerable daily variation in 17-ketosteroid output in the same individual, which may cause the level to vary in and out of the normal range.

A long list of conditions showed normal 17-ketosteroid excretion. These included hypogonadism, ovarian aplasia, gynecomastia, simple amenorrhea, oligospermia, obesity, alopecia and various psychiatric disorders.

FSH excretion was measured by bioassay and a definite end-point was more difficult to find. Occasionally it was necessary to test several specimens at various levels.

The excretion level of FSH was always high in ovarian aplasia when the patient was not receiving estrogenic therapy. This is one of the cardinal points in the clinical diagnosis of the condition. It was occasionally high in the male and female climacteric, seeming more consistent in the latter, in eunuchoidism, and in hyperthecosis. A high value was found in one female castrate.

A low level of FSH excretion was noted in patients with hypophyseal infantilism, Simmonds' disease and anorexia nervosa. The latter condition also shows normal levels, but unfortunately again, there was overlapping in the ranges with Simmonds' disease. Some eunuchoids also showed a low level of FSH excretion, and may represent a separate group from those with high values.

Normal values for FSH excretion were encountered in acromegaly, anorexia nervosa, hyperthyroidism, hypothyroidism, Cushing's syndrome, adrenal cortical hyperplasia, simple hirsutism, Addison's disease, gynecomastia, the climacteric, hyperthecosis, oligospermia, and alopecia.

The greatest clinical value of the test for 17-ketosteroids at present is in the high levels found in adrenal cortical hyperplasia and carcinoma, and the low levels of hypophyseal infantilism and Simmonds' disease.

The test for FSH is particularly valuable in its high levels in diagnosing ovarian aplasia and the climacteric. The low levels are of value in pituitary infantilism and Simmonds' disease.

The tests have resulted in a better understanding of some of the clinical syndromes and it is possible that further fractionation of the 17-ketosteroids may considerably increase their diagnostic importance.

ACKNOWLEDGMENT

The author gratefully acknowledges preliminary organization of the data by Dr. M. Goldberg and Dr. Leela Craig. Dr. Gilbert Gordan's assistance in reading and criticizing the finished manuscript was especially helpful.

BIBLIOGRAPHY

1. ZIMMERMANN, W.: Eine Farbreaktion der Sexualhormone und ihre Anwendung zur quantitativen colorimetrischen Bestimmung, Hoppe Seyler's Ztschr. f. physiol. Chem., 1935, ccxxxiii, 257–264.
2. INGRAM, C. H.: 17-Ketosteroids—a review of the literature, Bull. Univ. Maryland School Med., 1946, xxxi, 63–70.
3. ZONDEK, B.: Über die Hormone des Hypophysenvorderlappens. IV. Darstellung des Follikebreifungshormons (Prolan A)-Methodik der klinischen Harnanalyse zum Nachweis des Prolan, Klin. Wchnschr., 1930, ix, 1207–1209.
4. KLINEFELTER, H. F., ALBRIGHT, F., and GRISWOLD, G. C.: Experience with a quantitative test for normal or decreased amounts of follicle stimulating hormone in the urine in endocrinological diagnosis, Jr. Clin. Endocrin., 1943, iii, 529–544.
5. JUNGCK, E. C., MADDOCK, W. O., and HELLER, C. G.: Gonadotropic hormone: comparison of ultrafiltration and alcohol-precipitation methods of recovery from urine, Jr. Clin. Endocrin., 1947, vii, 1–10.

6. SMITH, P. H., ALBRIGHT, F., and DODGE, E.: Modifications in methods for the precipitation and assay of increased amounts of pituitary gonadotropic substances in the urine, Jr. Lab. and Clin. Med., 1943, xxviii, 1761–1766.
7. SIMPSON, M. E., LI, C. H., and EVANS, H. M.: Comparison of methods for standardization of pituitary interstitial-cell-stimulating hormone (ICSH), Endocrinology, 1942, xxx, 977–984.
8. GREEP, R. O., VAN DYKE, H. B., and CHOW, B. E.: Use of anterior lobe of prostate gland in the assay of metakentrin, Proc. Soc. Exper. Biol. and Med., 1941, xlvi, 644–649.
9. RIDDLE, O., BATES, R. W., and DYKSHORN, S. W.: The preparation, identification and assay of prolactin—a hormone of the anterior pituitary, Am. Jr. Physiol., 1933, cv, 191–216.
10. LYONS, W. R., and PAGE, E.: Detection of mammotropin in the urine of lactating women, Proc. Soc. Exper. Biol. and Med., 1935, xxxii, 1049–1050.
11. SIMPSON, M. E., EVANS, H. M., and LI, C. H.: Bioassay of adrenocorticotropic hormone, Endocrinology, 1943, xxxiii, 261–268.
12. SAYERS, G., SAYERS, M. A., LIANG, T., and LONG, C. N. H.: The effect of pituitary adrenotrophic hormone on the cholesterol and ascorbic acid content of the adrenal of the rat and the guinea pig, Endocrinology, 1946, xxxviii, 1–9.
13. ROWLANDS, I. W., and PARKES, A. S.: Quantitative study of the thyrotropic hormone of anterior pituitary extracts, Biochem. Jr., 1934, xxviii, 1829–1843.
14. DE ROBERTIS, E.: Intracellular colloid in the initial stages of thyroid activation, Anat. Rec., 1942, lxxxiv, 125–135.
15. DE ROBERTIS, E., and DEL CONTE, E.: Metodo citologico para la determinacion de la hormona tireotropa de la hipofisis, Rev. Soc. argent. de biol., 1944, xx, 88–99.
16. DVOSKIN, S.: Intracellular colloid droplets as a basis for thyrotrophic hormone assay in the chick, Endocrinology, 1947, xli, 220–229.
17. EVANS, H. M., SIMPSON, M. E., MARX, W., and KIBRICK, E.: Bioassay of the pituitary growth hormone. Width of the proximal epiphysial cartilage of the tibia in hypophysectomized rats, Endocrinology, 1943, xxxii, 13–16.
18. KAMM, O., ALDRICH, T. B., GROTE, I. W., ROWE, L. W., and BUGBEE, E. B.: The active principles of the posterior lobe of the pituitary gland. I. The demonstration of the presence of two active principles. II. The separation of the two principles and their concentration in the form of potent solid preparations, Jr. Am. Chem. Soc., 1928, I, 573–601.
19. GUTERMAN, H. S.: A human pregnancy test based upon a color reaction of pregnandiol in the urine, Jr. Clin. Endocrin., 1944, iv, 262–267.
20. GUTERMAN, H. S.: Further observations on the value of the pregnandiol test for pregnancy, Jr. Clin. Endocrin., 1945, v, 407–411.
21. REINHART, H. L., and BARNES, A. C.: An evaluation of the Guterman pregnancy test in clinical practice, Jr. Clin. Endocrin., 1946, vi, 664–667.
22. MACK, H. C., and PARKS, A. E.: The pregnandiol precipitation test. Clinical application of a rapid method for the diagnosis of pregnancy, Jr. Clin. Endocrin., 1947, vii, 351–363.
23. SHAPIRO, H. A., and ZWARENSTEIN, H.: A test for the early diagnosis of pregnancy on the South African clawed toad (*Xenopus laevis*), South Africa Med. Jr., 1935, ix, 202–205.
24. GALLI-MAININI, C.: Pregnancy test using the male toad, Jr. Clin. Endocrin., 1947, vii, 653–658.
25. ROBBINS, S. L., and PARKER, F.: The use of the male North American frog (*Rana pipiens*) in the diagnosis of pregnancy, Endocrinology, 1948, xlii, 237–243.
26. EDITORIAL: Adrenocortical hormones in human urine, Jr. Clin. Endocrin., 1943, iii, 655–656.
27. VENNING, E. H., KAZMIN, V. E., and BELL, J. C.: Biological assay of adrenal corticoids, Endocrinology, 1946, xxxviii, 79–89.

28. Venning, E. H., and Browne, J. S. L.: Excretion of glycogenic corticoids and of 17-ketosteroids in various endocrine and other disorders, Jr. Clin. Endocrin., 1947, vii, 79–101.
29. Venning, E. H., and Browne, J. S. L.: Effect of testosterone on the excretion of glycogenic corticoids, Jr. Clin. Endocrin., 1947, vii, 729–740.
30. Talbot, N. B., Albright, F., Saltzman, A. H., Zygmuntowicz, A., and Wixom, R.: The excretion of 11-oxycorticosteroid-like substances by normal and abnormal subjects, Jr. Clin. Endocrin., 1947, vii, 331–350.
31. Talbot, N. B., Saltzman, A. H., Wixom, R. L., and Wolfe, J. K.: The colorimetric assay of urinary corticosteroid-like substances, Jr. Biol. Chem., 1945, clx, 535–546.
32. Daughaday, W. H., Jaffe, H., and Williams, R. H.: Chemical assay for "cortin," Jr. Clin. Endocrin., 1948, viii, 166–174.
33. Smith, O. W., Smith, G. Van S., and Schiller, S.: The estrogens of urine from women: hydrolysis, separation and extraction, Endocrinology, 1939, xxv, 509–519.
34. Smith, G. Van S., Smith, O. W., and Pincus, G.: Total urinary estrogen, estrone and estriol during a menstrual cycle and pregnancy, Am. Jr. Physiol., 1938, cxxi, 98–106.
35. Jailer, J. W.: A fluorometric method for the determination of estrogens, Endocrinology, 1947, xli, 198–201.
36. Cohen, H., and Bates, R. W.: A simple quantitative colorimetric method for estrogenic steroids, Jr. Clin. Endocrin., 1947, vii, 701–707.
37. Venning, E. H., and Browne, J. S. L.: Isolation of a water-soluble pregnandiol complex from human pregnancy urine, Proc. Soc. Exper. Biol. and Med., 1936, xxxiv, 792–793.
38. Venning, E. H.: Gravimetric method for determination of sodium pregnandiol glucuronidate (an excretion product of progesterone), Jr. Biol. Chem., 1937, cxix, 473–480.
39. Funk, C., and Harrow, B.: The male hormone, Proc. Soc. Exper. Biol. and Med., 1929, xxvi, 325–326.
40. Funk, C., Harrow, B., and Lejwa, A.: The male hormone. II, Proc. Soc. Exper. Biol. and Med., 1929, xxvi, 569–570.
41. Tschopp, E.: Die physiologischen Wirkungen des Kunstlichen Männlichen-Sexualhormons (Androsteron), Klin. Wchnschr., 1935, xiv, 1064–1068.
42. Selye, H.: Textbook of Endocrinology, Acta Endocrinologica, Montreal, 1947, p. 611–612.
43. Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C.: Colorimetric assay of 17-ketosteroids in urine. A survey of the use of this test in endocrine investigation, diagnosis and therapy, Jr. Clin. Endocrin., 1941, i, 234–256.
44. Pincus, G.: A diurnal rhythm in the excretion of urinary ketosteroids by young men, Jr. Clin. Endocrin., 1943, iii, 195–199.
45. Forbes, A. P., Donaldson, E. C., Reifenstein, E. C., and Albright, F.: The effect of trauma and disease on the urinary 17-ketosteroid excretion in man, Jr. Clin. Endocrin., 1947, vii, 264–288.
46. Callow, N. H., Callow, R. K., Emmens, C. W., and Stroud, S. W.: Methods of extracting compounds related to the steroid hormones from human urine, Jr. Endocrin., 1939, i, 76–98.
47. Callow, N. H., Callow, R. K., and Emmens, C. W.: Colorimetric determination of substances containing the grouping—CH_2CO—in urine extracts as an indication of androgen content, Biochem. Jr., 1938, xxxii, 1312–1331.
48. Callow, N. H., Callow, R. K., and Emmens, C. W.: The effect of the administration of testosterone propionate on the urinary excretion of compounds allied to the steroid hormones, Jr. Endocrin., 1939, i, 99–107.
49. Frame, E. G., Fleischmann, W., and Wilkins, L.: The influence of a number of androgenic steroids on the urinary excretion of neutral 17-ketosteroids, Bull. Johns Hopkins Hosp., 1944, lxxv, 95–101.

50. Reifenstein, E. C., Forbes, A. P., Albright, F., Donaldson, E., and Carroll, E.: Effect of methyl testosterone on urinary 17-ketosteroids of adrenal origin, Jr. Clin. Invest., 1945, xxiv, 416–434.
51. Cuyler, W. K., Hirst, D. V., Powers, J. M., and Hamblen, E. C.: Effects of desoxycorticosterone acetate in 17-ketosteroid and pregnandiol excretions, Jr. Clin. Endocrin., 1942, ii, 373–376.
52. Talbot, N. B., and Butler, A. M.: Urinary 17-ketosteroid assays in clinical medicine, Jr. Clin. Endocrin., 1942, ii, 724–729.
53. Robbie, W. A., and Gibson, R. B.: Rapid clinical determination of urinary 17-ketosteroids, Jr. Clin. Endocrin., 1943, iii, 200–205.
54. Wooster, H.: A biometric study of total neutral 17-ketosteroid excretion in the normal adult male, Jr. Clin. Endocrin., 1943, iii, 483–492.
55. Nathanson, I. T., and Wilson, H.: Factors affecting colorimetric urinary 17-ketosteroid determinations, Endocrinology, 1943, xxxiii, 189–203.
56. Friedgood, H. B., Taylor, E. H., and Wright, M. L.: Combined versus independent hydrolysis and extraction of urinary 17-ketosteroids, Jr. Clin. Endocrin., 1943, iii, 638–647.
57. Drekter, I. J., Pearson, S., Bartczak, E., and McGavack, T. H.: A rapid method for the determination of total urinary 17-ketosteroids, Jr. Clin. Endocrin., 1947, vii, 795–800.
58. Talbot, N. B., Berman, R. A., MacLachlan, E. A., and Wolfe, J. K.: The colorimetric determination of neutral steroids (hormones) in a 24-hour sample of human urine (pregnandiol; total, alpha and beta alcoholic, and non-alcoholic 17-ketosteroids), Jr. Clin. Endocrin., 1941, i, 668–673.
59. Werner, S. C.: The daily variation in 17-ketosteroid excretion of men and women, Jr. Clin. Endocrin., 1941, i, 951–954.
60. Baumann, E. J., and Metzger, N.: Colorimetric estimation and fractionation of urinary androgens. Assays of normal and pathological urines, Endocrinology, 1940, xxvii, 664–669.
61. Salter, W. T., Cahen, R. L., and Sappington, T. S.: Urinary 17-ketosteroids in metabolism. II. Partition of gonadal and adrenocortical hormonal derivatives of normal, endocrine and cancerous patients, Jr. Clin. Endocrin., 1946, vi, 52–76.
62. Pincus, G.: The urinary ketosteroids—report of conference, Jr. Clin. Endocrin., 1943, iii, 301–303.
63. Dingemanse, E., Veld, G. H., and De Laat, B. M.: Clinical method for the chromatographic-colorimetric determination of urinary 17-ketosteroids, Jr. Clin. Endocrin., 1946, vi, 535–548.
64. Lieberman, S., Dobriner, K., Hill, B. R., Fieser, L. F., and Rhoads, C. P.: Studies in steroid metabolism. II. Identification and characterization of ketosteroids isolated from urine of healthy and diseased persons, Jr. Biol. Chem., 1948, clxxii, 263–295.
65. Burton, R. B., Zaffaroni, A., and Keutmann, E. H.: The application of partition chromatography to ketosteroids. Program Assoc. for the Study of Int. Secretions, thirtieth meeting, 1948, p. 51–52.
66. Pincus, G.: The analysis of human urines for steroid substances, Jr. Clin. Endocrin., 1945, v, 291–300.
67. Dobriner, K., Lieberman, S., and Rhoads, C. P.: Studies in steroid metabolism. I. Methods for the isolation and quantitative estimation of neutral steroids present in human urine, Jr. Biol. Chem., 1948, clxxii, 241–261.
68. Holtorff, A. F., and Koch, F. C.: The colorimetric estimation of 17-ketosteroids and their application to urine extracts, Jr. Biol. Chem., 1940, cxxxv, 377–392.
69. Talbot, N. B., Butler, A. M., Berman, R. A., Rodriguez, P. M., and MacLachlan, E. A.: Excretion of 17-ketosteroids by normal and by abnormal children, Am. Jr. Dis. Child., 1943, lxv, 364–375.

70. HOFFMAN, M. M.: The physiological and clinical significance of the urinary 17-ketosteroids, McGill Med. Jr., 1944, xiii, 177–188.
71. SUNDERMAN, F. W., and ROSE, E.: Studies in serum electrolytes. XVI. Changes in the serum and body fluids in anorexia nervosa, Jr. Clin. Endocrin., 1948, viii, 209–220.
72. LANDAU, R. L., KNOWLTON, K., ANDERSON, D., BRANDT, M. B., and KENYON, A. T.: The effect of starvation on urinary 17-ketosteroid excretion, Jr. Clin. Endocrin., 1948, viii, 133–145.
73. ENGSTROM, W. W., and MASON, H. L.: The excretion of 17-ketosteroids in patients with hyperthyroidism and myxedema, Jr. Clin. Endocrin., 1944, iv, 517–527.
74. BENDA, C. E., and BIXBY, E. M.: Urinary excretion of 17-ketosteroids in various conditions of oligophrenia correlated with some autopsy observations, Jr. Clin. Endocrin., 1947, vii, 503–518.
75. MILLER, S., and MASON, H. L.: The excretion of 17-ketosteroids by diabetics, Jr. Clin. Endocrin., 1945, v, 220–225.
76. KEPLER, E. J., and MASON, H. L.: Relation of urinary steroids to the diagnosis of adrenal cortical tumors and adrenal cortical hyperplasia: quantitative and isolation studies, Jr. Clin. Endocrin., 1947, vii, 543–558.
77. NATHANSON, I. T., and AUB, J. C.: Excretion of sex hormones in abnormalities of puberty, Jr. Clin. Endocrin., 1943, iii, 321–330.
78. LUFT, R.: On the determination of urinary 17-ketosteroids and its clinical significance, Acta med. Scandinav., 1943, cxv, 277–299.
79. ENGSTROM, M. W., MASON, H. L., and KEPLER, E. J.: Excretion of neutral 17-ketosteroids in adrenal cortical tumor and feminine pseudohermaphroditism with adrenal cortical hyperplasia, Jr. Clin. Endocrin., 1944, iv, 152–155.
80. RAICES, A. E., DEL CASTILLO, E. B., and GAMBIN, M.: Los 17-cetoesteroides en la virilizacion de la mujer adulta, Medicina, Buenos Aires, 1945, v, 152–170.
81. WARREN, F. L.: Estimation of urinary 17-ketosteroids in the diagnosis of adrenal cortical tumors, Cancer Res., 1945, v, 49–54.
82. HERWEG, J. C., ACKERMAN, L. V., and ALLEN, W. M.: The excretion of neutral 17-ketosteroids in two cases of male pseudohermaphroditism, Jr. Clin. Endocrin., 1946, vi, 275–282.
83. WILKINS, L.: A feminizing adrenal tumor causing gynecomastia in a boy of five years contrasted with a virilizing tumor in a five-year-old girl, Jr. Clin. Endocrin., 1948, viii, 111–132.
84. CALLOW, N. H., CALLOW, R. K., and EMMENS, C. W.: 17-Ketosteroid, androgen and oestrogen excretion in cases of gonadal or adrenal cortical deficiency, Jr. Endocrinol., 1940, ii, 88–98.
85. MCCULLAGH, E. P., SCHNEIDER, R. W., BOWMAN, W., and SMITH, M. B.: Adrenal and testicular deficiency. A comparison based on similarities in androgen deficiency, androgen and 17-ketosteroid excretion, and on differences in their effects upon pituitary activity, Jr. Clin. Endocrin., 1948, viii, 275–294.
86. KINSELL, L. W.: Spermatogenesis in a "pan-hypopituitary" eunuchoid, as a result of testosterone therapy, Jr. Clin. Endocrin., 1947, vii, 781–786.
87. HELLER, C. G., and NELSON, W. O.: Hyalinization of the seminiferous tubules associated with normal or failing Leydig-cell function. Discussion of relationship to eunuchoidism, gynecomastia, elevated gonadotropins, depressed 17-ketosteroids and estrogens, Jr. Clin. Endocrin., 1945, v, 1–12.
88. WALL, N. M., and HURXTHAL, L. M.: Eunuchoidism with excessive urinary 17-ketosteroids and response to testosterone therapy, Lahey Clin. Bull., 1946, iv, 231–237.
89. CATCHPOLE, H. R., HAMILTON, J. B., and HUBERT, G. R.: Effect of male hormone therapy on urinary gonadotropins in man, Jr. Clin. Endocrin., 1942, ii, 181–186.
90. HAMILTON, J. B., CATCHPOLE, H. R., and HAWKE, C. C.: Titers of gonadotropins in urine of aged eunuchs, Jr. Clin. Endocrin., 1945, v, 203–209.

91. Lisser, H., Curtis, L. E., Escamilla, R. F., and Goldberg, M. B.: The syndrome of congenitally aplastic ovaries with sexual infantilism, high urinary gonadotropins, short stature and other congenital abnormalities, Jr. Clin. Endocrin., 1947, vii, 665–687.
92. Nathanson, I. T.: Studies on the etiology of human breast disease. I. Urinary excretion of follicle-stimulating hormone, estrogens and 17-ketosteroids in adolescent mastitis of males, Jr. Clin. Endocrin., 1942, ii, 311–314.
93. Davison, R. A., Koets, P., and Kuzell, W. C.: Excretion of 17-ketosteroids in ankylosing spondylarthritis and in rheumatoid arthritis: a preliminary report, Jr. Clin. Endocrin., 1947, vii, 201–204.
94. Kinsell, L. W., Michaels, G. D., Li, C. H., and Larsen, W. E.: Studies in growth, I. Inter-relation between pituitary growth factor and growth-promoting androgens in acromegaly and gigantism. II. Quantitative evaluation of bone and soft tissue growth in acromegaly and gigantism, Jr. Clin. Endocrin., in press.

THE HEMODYNAMIC EFFECTS OF SYMPATHECTOMY IN ESSENTIAL HYPERTENSION *

By Robert W. Wilkins, M.D., James W. Culbertson, M.D., and Meyer H. Halperin, M.D., *Boston, Massachusetts*

Surgical sympathectomy has been employed so extensively for the treatment of essential hypertension that one might assume its hemodynamic effects to be completely understood. Quite to the contrary, however, very little is known concerning its direct vascular or indirect metabolic effects that will explain its success in some cases and its failure in others. Until these matters are fully understood the rationale for surgical treatment, and indeed for medical management, of essential hypertension must remain on an empirical basis. For this reason these problems have been and will continue to be the subject of long-term investigation in this laboratory.

Materials and Methods

Patients with essential hypertension selected for splanchnicectomy [1] have been made freely available for study through the active coöperation of Dr. Reginald H. Smithwick, under whose direction sympathectomy was performed. They were studied before and again, if possible within three weeks after bilateral operation, usually of the lumbodorsal type.[2] In addition, some patients were studied a third time four to 10 months after operation, whereas a few patients were studied only once—from one to nine years postoperatively.

Arterial pressure was measured with a Hamilton manometer [3] attached to a needle in the brachial or femoral artery. Cardiac output was determined by the Fick principle with the intravenous catheter method of Cournand.[4] Hepatic-portal (splanchnic exclusive of renal and adrenal) blood flow was estimated by the bromsulfalein method of Bradley et al.[5] Both before and after operation the patients, while under study, were given a number of vasomotor stimuli designed to produce, if possible, sympathetic nervous vasoconstriction.[6, 7] The most useful of these stimuli were (*a*) tilting the subject into the upright position and (*b*) having him perform the Valsalva maneuver.

Cardiac Output. Confirming the observations of others,[8, 9] no great or consistent change was found in basal cardiac output of patients after sympathectomy as compared with before, regardless of how much the arterial

* Presented before the Fifth General Session of the Twenty-ninth Annual Session of the American College of Physicians in San Francisco, California, April 23, 1948.

From the Robert Dawson Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

pressure was lowered (table 1). Thus, the cardiac output and mean * arterial pressure in three patients studied before *lumbodorsal splanchnicectomy* [2] averaged respectively 5.97 l./min. and 172 mm. Hg, and when repeated in the same patients two weeks after operation they averaged 5.37 l./min. and 142 mm. Hg. Furthermore, when measured a third time 10 months after operation the output in two of these patients again showed no consistent change. Likewise, cardiac output measured after *supradiaphragmatic splanchnicectomy* [12] in two patients, and after *transthoracic extension* [2] of a previous splanchnicectomy in two others, showed no consistent change from the preoperative values (table 1).

TABLE 1

Average Basal Cardiac Output (Direct Fick) and Arterial Pressure

Patient	Sex	Age	Surface Area sq. m.	Type of Operation†		Before Sympathectomy		After Sympathectomy			
								2 Weeks		10 Months	
				Previous	Present	Cardiac Output l./min.	Mean* Arterial Pressure mm.Hg	Cardiac Output l./min.	Mean* Arterial Pressure mm.Hg	Cardiac Output l./min.	Mean* Arterial Pressure mm.Hg
Far	F	41	1.55		LDS	7.07	147	5.54	139		
Bus	M	26	1.78		LDS	6.27	179	6.31	125	5.27	130
Pit	F	52	1.55		LDS	4.56	189	4.27	161	5.17	144
Dun	M	30	1.83		SDS	5.79	120	5.89	109		
Bro	M	51	1.79		SDS	3.89	202	4.39	150		
Cra	M	26	1.84	SDS	TTE	5.04	142	6.27	116		
Ret	M	41	2.05	LDS	TTE	7.24	173	6.22	162		
Mean		38	1.77			5.69	165	5.56	137	5.22	137

* One-half systolic plus diastolic, from direct readings with Hamilton manometer.
† LDS = lumbodorsal splanchnicectomy.
SDS = supradiaphragmatic splanchnicectomy.
TTE = transthoracic extension of previous splanchnicectomy upward to and including the first or second dorsal (thoracic) sympathetic trunk ganglia.

Hepatic-Portal Blood Flow. Basal blood flow through the liver as estimated by the hepatic extraction of bromsulfalein was uniformly increased in 10 patients shortly after sympathectomy except in one ("Max") of the seven in whom arterial pressure was already lowered (table 2).[10, 11] Thus, within three weeks following *lumbodorsal splanchnicectomy* hepatic blood flow in eight patients resting in a horizontal position had increased from an average of 1433 to 2018 ml. per minute per 1.73 sq. m. of body surface.† The mean arterial pressure in this group averaged 160 mm. Hg before and 149 mm. Hg shortly after operation. When measured four to seven months later in four

* Arithmetic mean, calculated simply as one-half the sum of the systolic and diastolic pressures.

† Subsequent values for hepatic-portal blood flow have been corrected likewise to standard body surface area of 1.73 square meters.

TABLE II

Average Basal Hepatic-Portal Blood Flow and Arterial Pressure in the Horizontal Position

Patient	Sex	Age	Before Sympathectomy		After Sympathectomy					
						Early (10–20 days)		Late (months or years)		
			HPBF ml./min./1.73 sq. m.	Mean* Arterial Pressure mm. Hg	Type of Operation†	HPBF ml./min./1.73 sq. m.	Mean* Arterial Pressure mm. Hg	Interval	HPBF ml./min./1.73 sq. m.	Mean* Arterial Pressure mm. Hg
								Mos.		
Dun	M	30	1040	120	SDS	2013	109			
Bro	M	51	1134	178	SDS	1363	146			
Max	M	43	1524	132 (s)	LDS	1309	111 (s)			
Pau	M	36	1960	124 (s)	LDS	2360	120 (s)			
She	M	51	1127	138 (s)	LDS	1810	157 (s)	4	1404	134 (s)
McC	M	43	1558	184 (s)	LDS	2884	184 (s)	6	1855	178 (s)
Dea	M	54	1334	168 (s)	LDS	2748	152 (s)	7	1454	184 (s)
Gol	M	31	944	178 (s)	LDS	1327	183 (s)	2	1168	181 (s)
								7	1314	167
Bus	M	26	1450	182	LDS	1857	128	10	813	131
Pit	F	53	1563	171	LDS	1851	154	10	1192	156
Oue	F	24	1397	166	TTS			4	1259	105
								Yrs.		
Yof	F	42			LDS			1	1169	132
Bar	F	52			LDS			2	896	153
Ret	M	41			LDS			3	1356	169
Dem	M	52			LDS			4	1318	176
Lee	M	35			LDS			4	866	110 (s)
O'L	F	47			LDS			9	1347	123

* One-half systolic plus diastolic pressure.
(s) Taken with mercury sphygmomanometer.
† TTS = total thoracic sympathectomy.
SDS = supradiaphragmatic splanchnicectomy.
LDS = lumbodorsal splanchnicectomy.

of these patients (in whom it had averaged 1241 ml. before, and 2192 ml. shortly after operation), the resting hepatic blood flow averaged 1507 ml./min. In this group the mean arterial pressure averaged 167, 169, and 166 mm. Hg during the first, second, and third tests respectively. In two patients who were not studied the third time until 10 months after operation the resting hepatic blood flow and mean arterial pressure respectively averaged 1507 ml./min. and 177 mm. Hg before, 1854 ml./min. and 141 mm. Hg shortly after, and 1003 ml./min. and 144 mm. Hg 10 months after the operation (figure 1).

In two patients in whom *supradiaphragmatic splanchnicectomy* was done hepatic blood flow and mean arterial pressure respectively averaged 1087 ml./min. and 149 mm. Hg before, and 1688 ml./min. and 128 mm. Hg shortly after operation. In one patient who had a *total thoracic sympathectomy* [2] the hepatic blood flow measured four months (but not earlier) after

operation had declined slightly from the preoperative average of 1397 ml./min. to 1259 ml./min. The mean arterial pressure in this patient had decreased markedly from a preoperative level of 166 mm. Hg to a postoperative value of 105 mm. Hg.

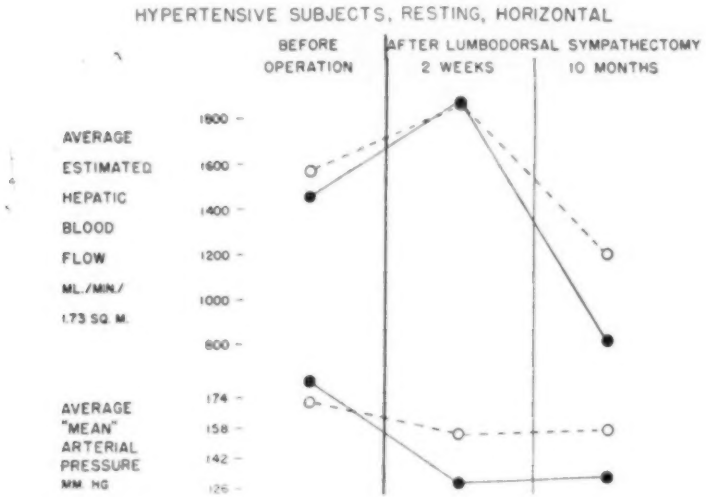


FIG. 1. Chart of average hepatic-portal blood flow and "mean" (one-half the systolic plus diastolic) arterial pressure in two patients—"Pit" (broken lines and circles) and "Bus" (solid lines and dots)—before and after lumbodorsal sympathectomy. Biopsy of the kidneys at operation in "Bus" revealed chronic glomerular nephritis.

Finally, six patients who were studied one to nine years after (but not before) lumbodorsal splanchnicectomy had mean arterial pressures that averaged 144 mm. Hg and hepatic blood flows that averaged 1159 ml./min., a value considerably below the average of 1490 ml./min. for 45 * normotensive patients[5] and slightly below the average of 1294 ml./min. for 25 unoperated hypertensive patients.[13] Thus, splanchnic vasodilatation apparently was present immediately after operation, whether or not the blood pressure was significantly affected, but over a period of months it slowly moderated.

Tilting the patient into the upright position caused hepatic blood flow in 12 unoperated hypertensive, as in normotensive, subjects consistently to decrease without a proportionate fall in arterial pressure[14] (table 3). This decrease in blood flow in the upright position before operation averaged 31 per cent but was accompanied by only a 2 per cent decrease in average mean arterial pressure. In five of these patients two weeks after the lumbo-

* Including 23 subjects from the paper cited, 14 additional subjects studied by Dr. Franz J. Ingelfinger, and 8 subjects studied in this laboratory.

TABLE III

Effects of Upright Posture on Average Basal Hepatic-Portal Blood Flow and Arterial Pressure

Patient	Sex	Age	Before Sympathectomy				After Sympathectomy				
			Horizontal		Upright			Horizontal		Upright	
			HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg	HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg	Interval	HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg	HPBF ml./min./ 1.73 sq. m.	Mean* Arterial Pressure mm. Hg
							Mos.				
Val	M	37	1328	161 (s)	900	157 (s)					
Ric	M	33	1205	175 (s)	752	173 (s)					
Cam	M	51	1120	167	1028	173					
Ayd	M	51	1403	162	981	161					
Col	M	28	941	174 (s)	632	160 (s)					
Dun†	M	30	1040	120	652	109	½	2013	109	878	90
Max	M	43	1524	132 (s)	782	126 (s)	½	1309	111 (s)	685	75 (s)
Pau	M	36	1960	124 (s)	990	123 (s)	1	2360	120 (s)	1593	80 (s)
Dea	M	54	1334	168 (s)	993	171 (s)	2	2748	152 (s)	1913	138 (s)
							7	1454	184 (s)	1187	169 (s)
She	M	51	1127	138 (s)	817	134 (s)	½	1810	157 (s)	1500	131 (s)
							4	1404	134 (s)	982	116 (s)
McC	M	43	1558	184 (s)	1330	185 (s)	½	2884	184 (s)	1625	133 (s)
							6	1855	178 (s)	1332	147 (s)
Gol	M	31	944	178 (s)	835	165 (s)	2	1168	181 (s)	927	149 (s)
							7	1314	167	1247	145
							Yrs.				
Bar	F	52					3	896	153	781	124
Lee	M	35					4	866	110 (s)	770	108 (s)

* One-half systolic plus diastolic pressure.
† "Dun" had supradiaphragmatic splanchnicectomy.
"Max" and following patients had lumbodorsal splanchnicectomy.
(s) Taken with mercury sphygmomanometer.

dorsal operation, when the hepatic blood flow in the horizontal position (as pointed out above) was greater than before, it tended to decrease in the upright position, but roughly in proportion with the postural fall in arterial pressure, 34 per cent and 23 per cent respectively.[15] Three of these patients studied four to seven months after operation showed a decrease in hepatic blood flow and arterial pressure in the upright position of 26 per cent and 13 per cent, respectively, as compared with the values in the horizontal position. However, collateral evidence indicated that in two, and probably in the third (figure 2), of these patients, splanchnic vasoconstrictor reflexes, though markedly reduced, were not completely abolished. Two patients studied for the first time three and four years after lumbodorsal splanchnicectomy had hepatic blood flows and mean arterial pressures in the horizontal position that averaged respectively 881 ml./min. and 133 mm. Hg. In the upright position these values fell to 776 ml./min. and 116 mm. Hg, decreases of 12 per cent and 13 per cent respectively.

Figure 2 illustrates the effects of splanchnicectomy upon the arterial pressure and the hepatic-portal blood flow of a hypertensive patient ("McC") in both the horizontal and upright positions. Before operation there was a fall in hepatic flow with little change in arterial pressure when the patient was tilted upright. Two weeks after operation, when there was a marked increase in hepatic blood flow and a slightly lower arterial pressure in the horizontal position, only a small decrease in average flow occurred with a striking fall of pressure in the upright position. Six months after operation resting hepatic blood flow had returned toward the pre-operative level and arterial pressure had shown little further change. When the patient was tilted upright, both the arterial pressure and the hepatic blood flow fell, but with a lower pressure the flow was as great as it had been before operation with a high pressure.

These results were interpreted as indicating that early after sympathectomy there was not only a splanchnic vasodilatation in the horizontal position, but also a marked reduction of splanchnic vasoconstriction in response to the upright position. Provided the splanchnic sympathectomy had been rela-

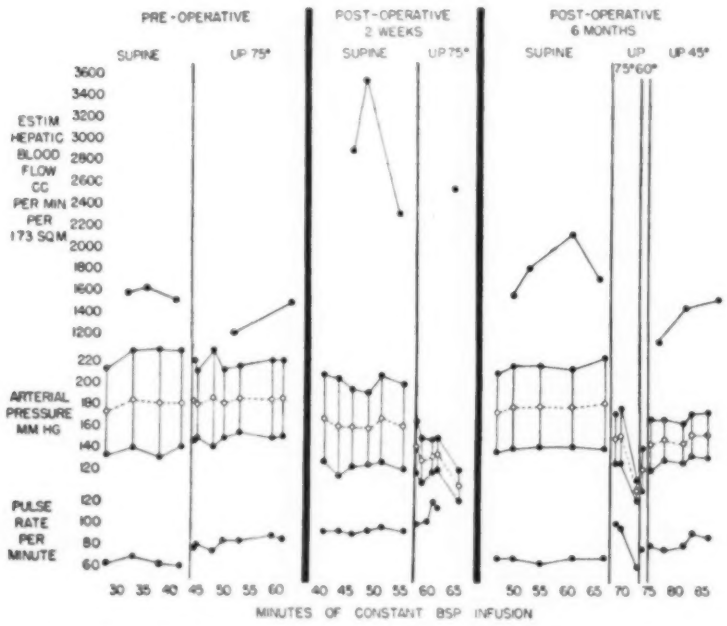


FIG. 2. Chart of estimated hepatic-portal blood flow (EHBF), arterial pressure, and pulse rate of a patient—"McC"—in the horizontal and upright positions, before and after lumbodorsal sympathectomy. During the third test the patient was unable to stand at 75 degrees long enough to allow EHBF to be measured and so was lowered to 45 degrees.

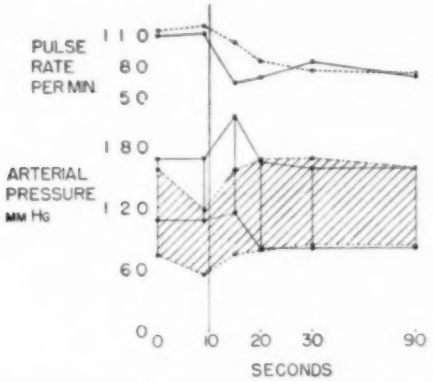


FIG. 3. Chart of the effects of being quickly tilted from the upright (75 degrees) to the horizontal position upon pulse rate and arterial pressure of a patient—"Pau"—before (solid lines and dots) and after (interrupted lines and circles) lumbodorsal sympathectomy.

tively complete, splanchnic vasoconstriction in response to the upright position apparently continued to be slight or absent months to years after the operation, when the early splanchnic vasodilatation had subsided.

Vasopressor Reflexes. By recording continuously the arterial pressure before, during and after certain simple vasopressor stimuli it has been possible to detect marked, though brief, reflex vasopressor responses that can be shown to be due largely to splanchnic vasoconstriction.[16, 17, 18] Thus, after the application of blood-pressure-lowering procedures such as a tilt into the

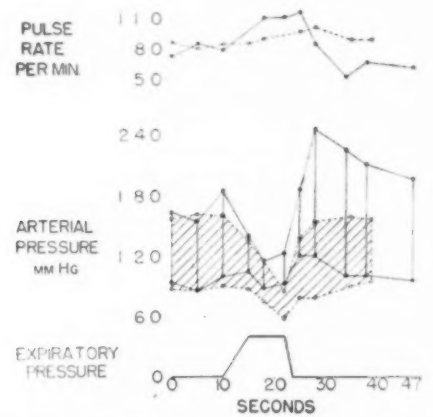


FIG. 4. Chart of the effects of the Valsalva maneuver (10 seconds of forced expiration) in the patient "Pau" before and after lumbodorsal sympathectomy. Other notations as in figure 3.

upright position (figure 3), or the performance of the Valsalva maneuver (figure 4), sharp hypertensive overshoots of arterial pressure were found immediately after stopping the stimuli. For example, upon stopping the Valsalva maneuver (during which venous return to and arterial output from the heart were temporarily diminished and arterial pressure markedly lowered), hypertensive patients, like normal subjects, usually markedly overshot their basal arterial pressures [6, 7] (figures 4, 5, 6).

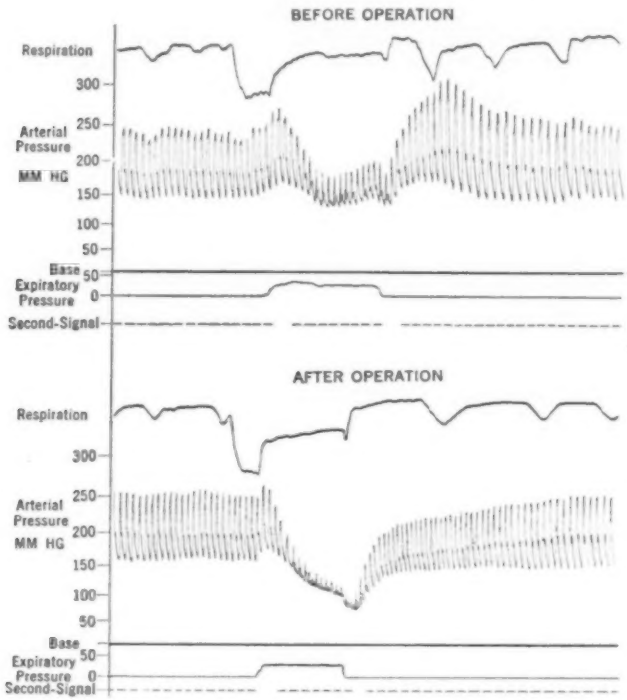


FIG. 5. Optical records of the effects of the Valsalva maneuver on respiration (inspiration down), arterial pressure, and expiratory pressure in a patient, "Rich," before and after lumbodorsal sympathectomy.

Such overshoots of arterial pressure in response to blood-pressure-lowering procedures were completely abolished or greatly reduced shortly after lumbodorsal splanchnicectomy (figures 3, 4, 5, 6). For example, the overshoot responses when graded in 20 patients (table 4) before this operation were grade IV in 4, grade III in 5, grade II in 9, and grade I in 2; whereas shortly after operation they were negative in all except two patients (grade I). Thus, even those patients who before sympathectomy had overshot

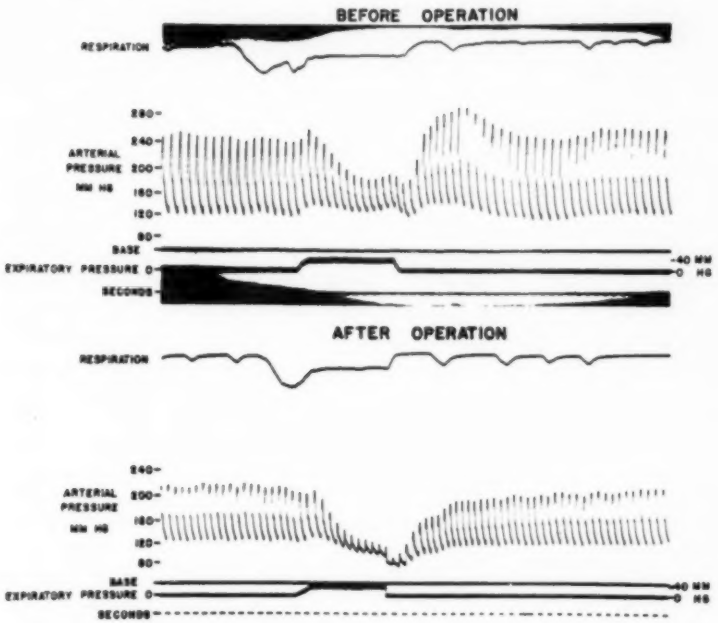


FIG. 6. Optical records of the effects of the Valsalva maneuver in patient "McCl" before and after lumbodorsal sympathectomy. Other notations as in figure 5.

their mean arterial pressures by as much as 35 per cent (grade IV), after sympathectomy had slight or negative (less than 5 per cent) overshoots following these stimuli, restoring their pressures only gradually (during 30 to 60 seconds) from the lowered to the control levels (figures 3, 4, 5, 6).[6, 7] Of 12 patients studied five months to nine years after (but not before) lumbodorsal splanchnicectomy, two had grade II, six had grade I, and four had negative responses (table 4).

The reduction or abolition by sympathectomy of such vasopressor overshoots after blood-pressure-lowering procedures seemed to depend upon the type and the amount of the sympathetic nervous tissue removed. Thus, operations less extensive than a lumbodorsal procedure usually failed to abolish the overshoots, while more extensive denervations added little to the effectiveness of the lumbodorsal operation in this regard.[7] Therefore, the amount of these overshoots was helpful in determining the extent and completeness of recent operations on the sympathetic nervous system and also in judging the continued effectiveness of old operations. For example, one patient ("McCl") who had recently undergone an operation elsewhere, presumably a supradiaphragmatic splanchnicectomy, had not been benefited in

TABLE IV

Overshoot Responses Graded before and/or after Lumbodorsal Splanchnicectomy

Patient	Sex	Age	Before Operation		Interval	After Operation	
			Arterial Pressure	Grade		Arterial Pressure	Grade
Tut	M	37	210/117	II	2 weeks	175/108	Neg.
Max	M	43	160/95	II	2 weeks	120/75	Neg.
Pau	M	36	165/95	IV	2 weeks	155/85	Neg.
Far	F	41	200/95	III	2 weeks	170/90	Neg.
Rich	F	29	245/140	III	2 weeks	250/160	Neg.
Yan	F	63	280/100	III	2 weeks	275/100	Neg.
Sil	F	23	170/110	IV	2 weeks	155/115	I
Swa	M	31	180/100	II	2 weeks	145/75	Neg.
Pea	M	35	190/110	I	2 weeks	125/75	Neg.
Goo	F	34	235/135	III	2 weeks	180/115	Neg.
Fie	M	32	170/110	II	2 weeks	135/85	Neg.
Bus	M	26	230/130	IV	2 weeks	165/95	Neg.
Fos	M	51	230/130	II	2 weeks	220/120	Neg.
Wat	M	50	215/120	I	2 weeks	150/90	Neg.
Pit	F	53	255/125	II	2 weeks	210/110	Neg.
Kon	M	50	205/110	III	2 weeks	165/90	Neg.
Nas	M	42	140/90	IV	2 weeks	140/75	Neg.
McCl	F	50	230/120	II	2 weeks	210/120	Neg.
Hur	M	21	220/125	II	2 weeks	180/110	I
Gol	M	31	230/135	II	2 months	240/145	Neg.
She	M	51	205/120 (s)		5 months	155/95	I
Dea	M	54	200/110 (s)		6 months	195/100	I
Yof	F	42	185/110 (s)		1 year	165/100	II
Bar	F	52	200/100 (s)		2 years	200/90	Neg.
Abe	F	35	185/130 (s)		2½ years	225/125	I
Dow	M	44	195/120 (s)		3 years	220/120	I
Ret	M	41	185/120 (s)		3 years	220/130	Neg.
Cha	F	37	165/100 (s)		4 years	135/75	I
Dem	M	52	225/125 (s)		4 years	230/110	Neg.
Lyn	M	42	175/130 (s)		4½ years	145/90	II
Sul	M	52	210/140 (s)		6 years	175/120	Neg.
O'L	F	47	140/90 to 180/120 (s)		9 years	145/85	I

(s) As reported, taken with sphygmomanometer.

any way. When tested, the patient was found to have grade II, or definite, overshoots after the vasopressor stimuli (figure 6). Upon reoperation it was discovered that the scar tissue of the previous wounds did not extend to the sympathetic chains, which were fully intact. A routine lumbodorsal splanchnicectomy was therefore performed, whereupon the overshoot responses to the same stimuli became negative. It was also interesting and helpful to observe in patients studied years after extensive resection of sympathetic nerves supplying the splanchnic region that the vasopressor overshoots were absent or of a low order as compared with those in unoperated hypertensive patients, although they were somewhat greater than those found early after splanchnicectomy.

The degree of vasopressor reactivity present before, or remaining after,

sympathectomy could not be directly correlated with the level of basal arterial pressure. This reactivity might be slight in preoperative, or completely negative in postoperative patients with fixed high basal arterial pressures; and it might be of the most marked type in normotensive individuals, or in unoperated hypertensive patients with only moderately elevated basal arterial pressures.[6, 7]

Discussion

Since there are no consistent changes in cardiac output after sympathectomy such changes obviously do not explain any fall or lack of fall, in basal arterial pressure that may occur. Thus, it cannot be argued that a postoperative reduction of pressure is caused by a depressed cardiac output due to inadequate venous return.[19] Nor can it be said that a lack of fall of arterial pressure is caused by a compensatory rise in cardiac output in response to a decrease in peripheral resistance.

Furthermore, if there is a considerable change in blood flow in any peripheral area after sympathectomy, it must be offset by an opposite change in some other area or cardiac output would not remain the same. But, since no great change in blood flow has been found in any organ, even the liver, when arterial pressure has been lowered and become stabilized after sympathectomy, one must assume that there has been a widespread decrease in peripheral resistance to account for the lowering of pressure. Even when there is a large increase in blood flow through the liver with no fall in arterial pressure shortly after sympathectomy, the total peripheral resistance must be nicely adjusted, since cardiac output is unchanged. Such adjustments suggest a high order of integration of the total peripheral blood flow (represented measurably by the cardiac output), whether or not the arterial pressure is lowered after sympathectomy.

Investigators who have studied renal hemodynamics by clearance methods in hypertensive patients [8, 19, 20, 21, 22, 23, 24] seem agreed that there are no significant changes in renal blood flow following splanchnicectomy. Therefore, they have found it difficult to attribute any fall in arterial pressure that may occur after such operations to a change in the *effective renal circulation*. There remains a possibility that the renal extraction of the clearance substances used in these studies may not be the same before and after sympathectomy, so that calculations based upon an assumed unchanged extraction may not represent accurately the *total renal hemodynamics*.[25] This possibility is now under study in this laboratory.[26]

It may be argued that if renal blood flow is maintained when arterial pressure is lowered after sympathectomy, it is because of "autonomous" adjustments [27] in the renal vasculature resulting in a decrease in renal resistance.[28] Thus, an undiminished renal blood flow would simply represent an adaptive response to, and in no sense a cause of, the reduction in arterial pressure. But from the data so far available it may be argued with equal

logic that arterial pressure may be reduced after sympathectomy, if, despite this reduction, renal blood flow can be maintained by means of a release of renal arteriolar constriction,[29] presumably by the sympathectomy. In this view the reduction in arterial pressure would be contingent upon an undiminished renal blood flow. The two arguments differ not only in their relative emphasis upon renal blood flow and renal resistance,[30] but also in their implications as to the cause-and-effect relationships of these two factors and the arterial pressure. Certainly the whole matter is still open to question, and for that reason it is now being reviewed in this laboratory.[26]

Contrary to the results in the kidney, the findings reported here on blood flow through the liver have demonstrated a definite hepatic-portal vasodilatation to occur early after sympathectomy, whether or not the arterial pressure is lowered. As time goes on this vasodilatation seems to subside. Therefore, it is difficult to explain any change, or lack of change, in arterial pressure as due directly to hepatic-portal vasodilatation. Possibly in some patients it may furnish a more adequate supply of oxygen and/or other materials for hepatic (or other splanchnic visceral) metabolism and so indirectly affect the production or alteration of substances involved in the elevation of arterial pressure.[31] This possibility also is now being investigated by studying the hepatic-portal consumption of oxygen, conjugation of para-amino hippuric acid, and extraction of mannitol and other substances from the blood.[32]

The great reduction, or abolition, by sympathectomy of splanchnic vasoconstrictor responses to stimuli like the upright position may be of even greater importance than the increase in resting hepatic blood flow per se, since apparently it persists after the increase in hepatic blood flow has subsided. Again, however, such vasodilatation (or absence of vasoconstriction) in the upright, as in the horizontal position, cannot be accepted as the direct explanation for any lowering of basal arterial pressure that may develop after sympathectomy, since it is found even when the arterial pressure remains elevated.

Likewise, reduction or abolition of reflex vasopressor overshoots of arterial pressure after blood-pressure-lowering procedures and their substitution by a more stable, or gradual, homeostatic mechanism may be a very important hemodynamic effect of sympathectomy. Before operation, even in response to the relatively mild stimuli used, peaks of arterial pressure in excess of 300 mm. Hg were frequently reached in some patients. Though of brief duration they conceivably could cause vascular rupture or other serious damage. Therefore, in such hypertensive patients, especially those with high levels of basal arterial pressure, it may be advisable to abolish these overshoots even when the basal levels of arterial pressure cannot be changed by surgical intervention. Indeed, the symptomatic improvement in many patients who have had no significant lowering of basal arterial pressure after sympathectomy may be due to the amelioration of this type of vascular strain.

Comparative measurements of overshoot responses to blood-pressure-

lowering procedures pre- and postoperatively in the same patient have furnished assays of sympathetic vasopressor activity that thus far have correlated well with the type and extent of the operation performed. Whether they will also correlate with other estimates of sympathetic vasopressor activity that may be used to predict the effectiveness of surgical sympathectomy in different patients remains to be seen. Already they have proved to be of positive value in the sense that when the overshoots were marked, a large portion, if not all, of the splanchnic sympathetic nerve supply was found intact at operation, and if extensively removed resulted in the disappearance or great reduction of the overshoots. Furthermore, completely negative responses have as yet been obtained only in sympathectomized subjects. However, small (grade I) preoperative responses have been recorded occasionally in hypertensive patients in whom apparently normal sympathetic nerves were found at operation.

It seems fair to conclude that none of the direct hemodynamic effects so far discovered in the sympathectomized areas of hypertensive patients adequately explains the effectiveness of the operation in lowering the basal arterial pressure in some individuals, as contrasted with its failure in others. For, while the sympathetic nervous system seems obviously involved in the hypertension of some patients, since the removal of large parts of it results in a lowering of the pressure, in other patients indistinguishable from these preoperatively by the methods now at hand, the sympathetic nervous system seems at the time of operation as obviously not the dominant factor, since its removal causes little or no change in pressure. But in both groups the purely hemodynamic effects (except upon overall peripheral resistance) are similar and are not sufficient in themselves to account for any change in pressure that may occur. Therefore, the *direct hemodynamic effects* of sympathectomy appear to be non-specific, but it is entirely possible that in some patients these changes may act through *indirect physical or chemical mechanisms* to lower the basal arterial pressure some months later, if not immediately after operation.

These considerations, and others derived from collateral studies on the effects of hypotensive drugs in hypertensive patients [33, 34, 35, 36, 37, 38] have led to the working hypothesis in this laboratory that the elevated basal arterial pressure of hypertensive patients is regulated by an intricate and highly integrated mechanism that is probably controlled through the central nervous system. It seems possible that essential hypertension may result from a varied succession of events—psychological, neurological, metabolic, humoral and/or physical—that tend, at first intermittently, and later continuously, to raise the arterial pressure. Eventually, perhaps as an adaptive process, the central integrating mechanism controlling the basal arterial pressure may become set at a higher level, establishing a sort of vicious circle. Furthermore, it is possible that the number of inciting and/or perpetuating factors may increase or decrease as time goes on, so that in some patients only one, while in others a combination of them, may be acting to sustain the

elevation of arterial pressure. Therefore, in order to lower the pressure in some patients it may be necessary to correct only one of these factors, while in others it may require a number of different therapeutic procedures applied successively or simultaneously.

Such a concept, rather than a unitarian theory, seems to satisfy the known facts concerning the nature and the relief of essential hypertension in man. Thus, sympathectomy alone will correct the hypertension in some patients. Likewise, a salt-free diet will lower the pressure in others. However, it now appears that these two procedures together are more apt to lower the pressure than either one used alone.[39] Similarly, each of the fundamentally different drugs, veratrum viride [33] and dihydroergocornine,[34] used alone may lower the pressure in certain hypertensive patients; but together they will lower the pressure in selected patients that neither one alone will affect.[38] Finally, three or even all four of the treatments mentioned above have been used simultaneously with success in a few patients who had failed to respond satisfactorily to any other single or combined form of therapy.

While such results may be explained as due simply to the additive effects of several non-specific hypotensive procedures and agents, they may denote the multiform nature of the hypertensive disease in some patients. For, when there is a significant and persistent lowering of the basal arterial pressure unaccompanied by signs of collapse or by toxic or unphysiologic side reactions, it may be postulated that the central integrating mechanism for regulating the arterial pressure has been reset at a lower level. Whatever the explanation, it has seemed most worthwhile to persist in trials of single agent or combination therapy in such patients because the palliative results, measured by objective criteria, so far observed have been highly gratifying, even in some of the most severe and chronic of cases. Even if "symptomatic," such therapy is warranted until it is definitely known whether essential hypertension is a single disease or merely a manifestation of several different diseases, until the inciting causes and perpetuating mechanisms in every type of case are understood, and until effective specific methods of treatment are freely available. These things will come only through continued research.

Summary

Laboratory studies of the hemodynamic effects of sympathectomy in hypertensive patients have revealed (1) little change in basal cardiac output (direct Fick method), (2) an early increase and later moderation in hepatic-portal blood flow (BSP method), (3) a decrease in the splanchnic vasoconstrictor response to the upright position, and (4) a decrease or abolition of vasopressor overshoots of arterial pressure after depressor procedures. The postoperative effects are similar whether or not arterial pressure is lowered, except that hepatic-portal blood flow apparently is influenced directly by the level of the arterial pressure.

These results, along with the reported studies on renal blood flow, in-

dicate that the direct hemodynamic effects of splanchnicectomy do not account for any lowering of arterial pressure that may occur. However, it is entirely possible that in some patients indirect physical or chemical mechanisms resulting from these hemodynamic effects may in time act to cause a widespread decrease in peripheral resistance and a lowering of arterial pressure.

Acknowledgment. The authors are grateful to Miss Adele Rymut, A.B., Miss Gretchen Baum, B.S., and Mrs. Gloria Kligler, B.A., for valuable assistance in preparation of tables and illustrations and to Miss Jane Holbrook, A.B., for the photographic reproductions.

BIBLIOGRAPHY

1. Smithwick, R. H.: The surgical treatment of continued hypertension, Jr. Med. Soc. New Jersey, 1947, xliv, 304–316.
2. Smithwick, R. H.: Surgery of the autonomic nervous system. Cole's Operative Technic. In press. Appleton-Century Co., New York.
3. Hamilton, W. F., Brewer, G., and Brotman, I.: Pressure pulse contours in the intact animal. I. Analytical description of a new high-frequency hypodermic manometer with illustrative curves of simultaneous arterial and intracardiac pressures, Am. Jr. Physiol., 1934, cvii, 427–435.
4. Cournand, A., and Ranges, H. A.: Catheterization of the right auricle in man, Proc. Soc. Exper. Biol. and Med., 1941, xlvi, 462–466.
5. Bradley, S. E., Ingelfinger, F. J., Bradley, G. P., and Curry, J. J.: The estimation of hepatic blood flow in man, Jr. Clin. Invest., 1945, xxiv, 890–897.
6. Wilkins, R. W., and Culbertson, J. W.: The effects of surgical sympathectomy upon certain vasopressor responses in hypertensive patients, Trans. Assoc. Am. Phys., 1947, lx, 195–207.
7. Wilkins, R. W., Culbertson, J. W., and Smithwick, R. H.: The effects of various types of sympathectomy upon vasopressor responses in hypertensive patients, Surg., Gynec. and Obst., 1948, lxxxvii, 661–668.
8. Adams, W., Alving, A. S., Sandiford, I., Grimson, K. S., and Scott, C.: The effect of bilateral paravertebral sympathectomy on the cardiorenal system in essential hypertension, Am. Jr. Physiol. (Proceedings), 1941, cxxxiii, 190–191.
9. Smith, E. L., Haynes, B. W., and Evans, E. I.: The effect of sympathectomy and tilting on arterial blood pressure, cardiac output and right atrial pressure in man, Federation Proc., 1946, v, 97.
10. Wilkins, R. W., Culbertson, J. W., and Ingelfinger, F. J.: The effects of splanchnicectomy upon hepatic function and blood flow in hypertensive patients, Jr. Clin. Invest., 1947, xxvi, 1200.
11. Wilkins, R. W., and Culbertson, J. W.: The effects of splanchnicectomy upon hepatic-portal blood flow in resting hypertensive patients. In preparation.
12. Peet, M. M.: Splanchnic section for hypertension, Univ. Hosp. Bull., Ann Arbor, 1935, i, 17–18.
13. Culbertson, J. W., and Wilkins, R. W.: The hepatic-portal blood flow in resting hypertensive patients. In preparation.
14. Culbertson, J. W., Wilkins, R. W., Ingelfinger, F. J., and Bradley, S. E.: The effect of the upright posture upon hepatic blood flow in normal and hypertensive human subjects, Jr. Clin. Invest., 1947, xxvi, 1178.
15. Wilkins, R. W., Culbertson, J. W., and Ingelfinger, F. J.: The effect of splanchnicectomy in hypertensive patients upon hepatic-portal blood flow in the upright as contrasted with the horizontal position. In preparation.
16. Wilkins, R. W., Hunt, J. S., and Friedland, C. K.: The effects of sudden changes in peripheral circulation upon cardiac output, Jr. Clin. Invest., 1942, xxi, 625–626.

17. WILKINS, R. W., FRIEDLAND, C. K., and BRADLEY, S. E.: Estimations of cardiac and vasomotor reserve, especially in response to strains designed to simulate those of acceleration, National Research Council, C. A. M. Report No. 177, 1943.
18. WILKINS, R. W., and FRIEDLAND, C. K.: Laryngeal epilepsy due to increased intrathoracic pressure, Jr. Clin. Invest., 1944, xxiii, 939.
19. CORCORAN, A. C., and PAGE, I. H.: Renal blood flow and sympathectomy in hypertension, Arch. Surg., 1941, xlii, 1072–1082.
20. SELZER, A., and FRIEDMAN, M.: Effect of bilateral splanchnicectomy upon renal blood flow in hypertension, Proc. Soc. Exper. Biol. and Med., 1941, xlviii, 429–431.
21. FINDLEY, T., CLINTON, E., and EDWARDS, J. C.: The effect of sympathectomy on renal blood flow in essential hypertension, Surgery, 1942, xii, 64–67.
22. FOÀ, P. P., WOODS, W. W., PEET, M. M., and FOÀ, N. L.: Effective renal blood flow, glomerular filtration rate and tubular excretory mass in arterial hypertension. II. Effect of supradiaphragmatic splanchnicectomy with lower dorsal sympathetic ganglionectomy, Arch. Int. Med., 1943, lxxi, 357–369.
23. TALBOTT, J. H., CASTLEMAN, B., SMITHWICK, R. H., MELVILLE, R. S., and PECORA, L. J.: Renal biopsy studies correlated with renal clearance observations in hypertensive patients treated by radical sympathectomy, Jr. Clin. Invest., 1943, xxii, 387–394.
24. GOLDRING, W., and CHASIS, H.: Hypertension and hypertensive disease, 1944, The Commonwealth Fund, New York, p. 156.
25. TRUETA, J., BARCLAY, A. E., DANIEL, P. M., FRANKLIN, K. J., and PRICHARD, M. M. L.: Studies of the renal circulation, 1947, Charles C. Thomas, Springfield.
26. CULBERTSON, J. W., BURNETT, C. H., and WILKINS, R. W.: Unpublished data.
27. SMITH, H. W., ROVENSTINE, E. A., GOLDRING, W., CHASIS, H., and RANGES, H. A.: The effects of spinal anesthesia on the circulation in normal unoperated man with reference to the autonomy of the arterioles and especially those of the renal circulation, Jr. Clin. Invest., 1939, xviii, 319–341.
28. BRADLEY, S. E.: Physiology of essential hypertension, Am. Jr. Med., 1948, iv, 398–415.
29. HOOBLER, S. W., MOE, G. K., RENNICK, B. R., NELIGH, R. B., and LYONS, R. H.: The effect of autonomic blockade with tetraethylammonium on the renal circulation in dogs and in normal and hypertensive patients, Univ. Hosp. Bull., Ann Arbor, 1947, xiii, 9–10.
30. LANDOWNE, M., and ALVING, A. S.: Renal resistance in "essential" hypertension. Relation to the effect of sympathectomy on blood pressure, Proc. Soc. Exper. Biol. and Med., 1948, lxvii, 115–118.
31. SHORR, E., ZWEIFACH, B. W., FURCHGOTT, R. F., and BAEZ, S.: Hepato-renal vasotropic factors in experimental shock and renal hypertension, Trans. Assoc. Am. Phys., 1947, lx, 28–51.
32. CULBERTSON, J. W., HALPERIN, M. H., and WILKINS, R. W.: Unpublished observations.
33. FREIS, E. D., and STANTON, J. R.: A clinical evaluation of veratrum viride in the treatment of essential hypertension, Am. Heart Jr., 1948, xxxvi, 723–738.
34. FREIS, E. D., STANTON, J. R., and WILKINS, R. W.: The effects of certain dihydrogenated alkaloids of ergot in hypertensive patients, Am. Jr. Med. Sci., 1948, ccxvi, 163–171.
35. FREIS, E. D.: Recent advances in the medical treatment of essential hypertension with particular reference to drugs, Med. Clin. North America, 1948, xxxii, 1247–1258.
36. WILKINS, R. W., FREIS, E. D., and STANTON, J. R.: Laboratory studies in man of drugs recently introduced for the relief of essential hypertension, Jr. Am. Med. Assoc. In press.
37. FREIS, E. D., STANTON, J. R., CULBERTSON, J. W., LITTER, J., HALPERIN, M. H., BURNETT, C. H., and WILKINS, R. W.: The hemodynamic effects of veratrum viride in man, Jr. Clin. Invest. In press.
38. WILKINS, R. W., FREIS, E. D., and STANTON, J. R.: The treatment of essential hypertension with veratrum viride and with dihydroergocornine. In preparation.
39. KINSEY, D., and SMITHWICK, R. H.: Unpublished observations.

RESULTS OF HIGH DORSOLUMBAR SYMPATHECTOMY FOR HYPERTENSION *

By James A. Evans, M.D., F.A.C.P., and Carl C. Bartels, M.D.,
Boston, Massachusetts

It has been the custom at the Lahey Clinic for the medical department to choose and recommend certain hypertensive patients for dorsolumbar sympathectomy as well as to follow their postoperative and subsequent course. This report is an attempt on our part to evaluate the results of operation in a strictly critical and unbiased manner based upon a six month to three year follow-up on 173 patients who had sympathectomies to include the fourth thoracic level.

Our first series of 54 cases in which resection was carried out to the eleventh or twelfth thoracic level, reviewed by E. C. Bartels [1] in 1942, showed that only 37 per cent of patients with hemorrhagic ocular fundi and moderately fixed blood pressure (Keith-Wagener Group III) were benefited. His experience led him to evolve a set of very strict criteria for selection of cases for operation, so much so that the criteria were criticized on the basis that such patients should have a good prognosis for at least the five-year reported period, and that perhaps surgery was not justified in many of the mild cases. The patients in Group III with hemorrhagic fundi, 80 per cent of whose life expectancy will not exceed four years (Keith and Wagener), were thus left hopeless (figure 1). In an attempt to benefit this group of

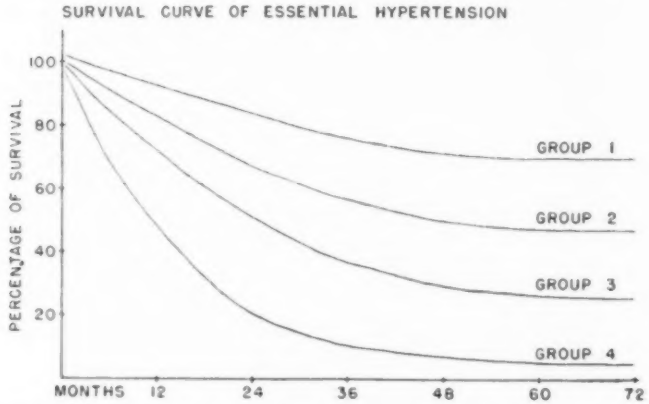


Fig. 1. Survival curve of essential hypertension (Keith, Wagener and Barker).

* Read at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 23, 1948.
From the Lahey Clinic.

patients and those in Group II with moderate cardiovascular renal changes whom we had been rejecting, sympathectomy was gradually raised from the twelfth thoracic to the third or fourth thoracic ganglion (figures 2 and 3). Poppen, who performed these operations, reported his results during this gradual rise in 1947.[2] Good and fair results in Grade III patients rose from 37 per cent to 63 per cent in a group whose operations ranged in extent from the eleventh thoracic to the fourth thoracic ganglion.

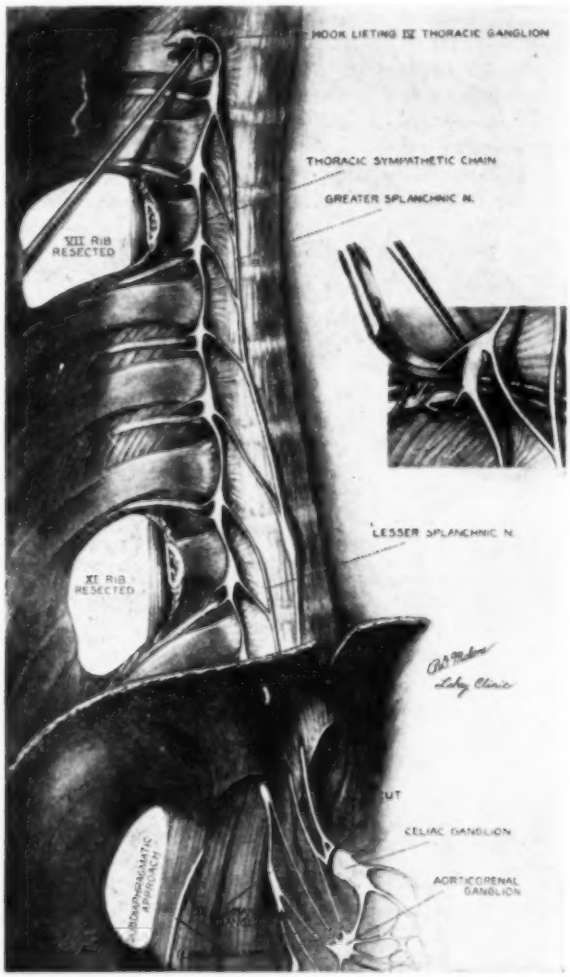


FIG. 2. The Poppen dorsolumbar sympathectomy and splanchnicectomy for hypertension.

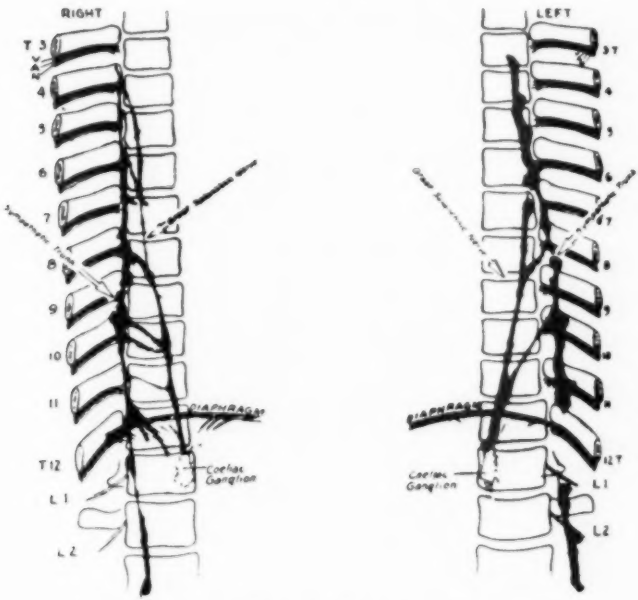


FIG. 3. Surgical specimens superimposed on drawing.

Experience with three patients with recurrent hypertension who had a second operation has supported us in our decision to raise the level of sympathetic resection. Branches to the splanchnic nerves always arise from the seventh thoracic and sometimes from as high as the third thoracic ganglions. Although the greater and lesser splanchnic nerves were cut at the level of the diaphragm in the seventh or twelfth thoracic to the third lumbar type of operation, these branches were found to have grown down again, reforming an amputation neuroma at the site of the celiac ganglion in all three cases (figure 4). In one case the growth was found to surround a silver clip left at the previous operation. The first operation had been at the level of the twelfth, eighth and seventh thoracic ganglions, seven, five and four years before, respectively. Sweat tests (figure 5) showed the sympathetics to the leg had not regenerated. Reoperation resulted in further drop in blood pressure in two patients. This led us to conclude that the splanchnic nerves constitute the most important area to be resected for decrease in blood pressure. A recent report from Smithwick's [3] group supports this contention.

It is difficult to test for splanchnic regeneration. Theoretically, there should be absence of abdominal visceral pain following splanchnicectomy, but only recently two patients have exhibited severe abdominal pain within

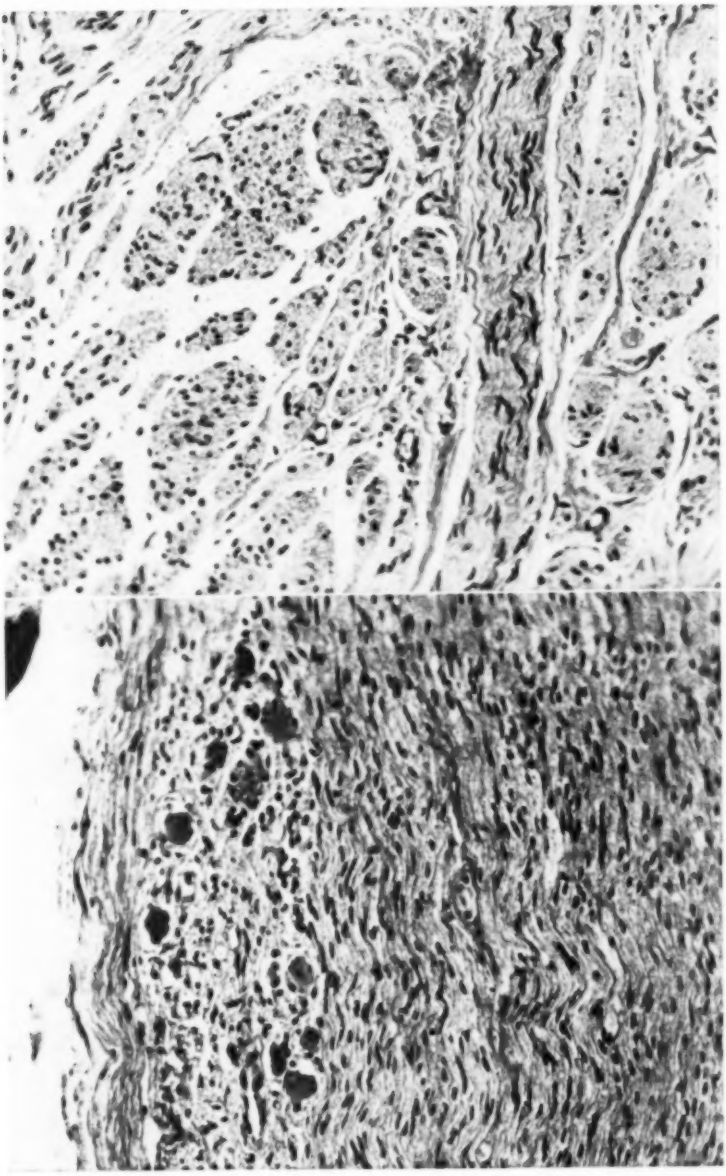


FIG. 4. Left, normal sympathetic ganglion and fibers. Right, amputation neuroma at site of celiac ganglion resected four years previously.

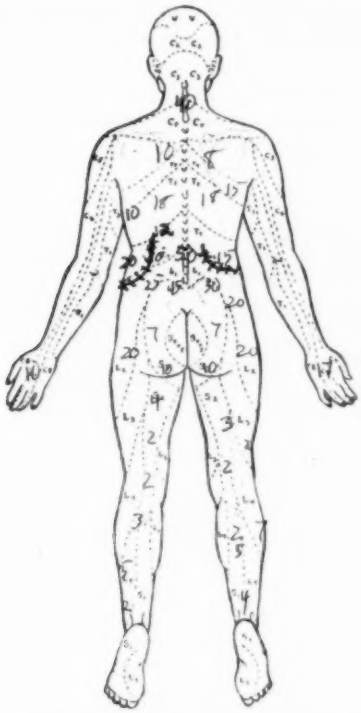


FIG. 5. Sweat test. This patient had a resection to the twelfth thoracic ganglion only, seven years before reoperation and the splanchnics cut at the celiac ganglion. The low figures show the minute current transmitted by the dry resistant skin in the legs which remain sympathectomized, yet the splanchnics were found regenerated at operation.

a few days after operation, one from gall-bladder disease and the other from an irritable spastic colon, without any sign of peritoneal irritation to account for the pain. Studies are being carried out with balloon distention of the gut and in one patient in whom this test was made no pain was experienced, yet at reoperation regeneration of the splanchnic nerves was found. Such regrowth of the thoracic sources of the splanchnics down into the celiac area, however, is only suggestive evidence of the necessity of resecting the splanchnics to their point of transit through the thoracic ganglions. We have no histologic or physiologic proof as yet that these new preganglionic fibers have actually established synapses in the celiac ganglion and are again functioning.

It must be stated *a priori* from our point of view as internists that we cannot accept six month to three year follow-ups in a chronic disease such as hypertension with any notion of forming reliable conclusions. To promise a patient of 30 with hypertension that he will live to the age of 70, an ex-

panse of 40 years, is as yet absurd. We are not even in a position to predict that patients with Grade III hypertension will exceed the 20 per cent expectation of surviving four years. All we can hope is that the observed reversal of retinal arterial changes toward normal, the frequent reduction in heart size and the improvement of kidney function should prolong life. We must wait 20 years for data in Group II cases, and 10 years in Group III cases to demonstrate that this procedure will check cardiovascular renal degenerative disease. In this regard Palmer [4] has stated there is a law of diminishing returns the longer the follow-up, from two thirds good results at the end of one year to 25 per cent at the end of three years, including all grades of hypertension. He also stated that a comparative group of 100 patients treated medically over three years had only half the number of good results.

High dorsolumbar sympathectomy has led us to reverse our criteria for the selection of patients. Formerly, we only thought, "Is this case mild enough with little enough cardiovascular degeneration to promise a good result?" The former operation was a comparatively less formidable procedure, possible, as Peet does it, in one stage, and required a comparatively short convalescent period of one to three months. Our present operative procedure has not resulted in raising the operative mortality rate. Three and a half to five weeks' hospitalization for a two-stage operation is necessary. Full economic recovery has required an average of five and a half months' convalescence for those patients now back at work. Nineteen patients were not back at work after one year. Much pain may be experienced for two to four months.

The main effect on the blood pressure is a profound orthostatic hypotension. In the first six months we have often substituted only one disease for another, namely, orthostatic hypotension for hypertension. This hypotension routinely requires a special corset with a spring suprapubic pad and elastic leg support (figure 6). In 19 cases we have had to resort to special pneumatic leggings patterned after the G-suit * of our aviators (figure 7). This device has enabled such patients to return immediately to at least part time work and has been worn for periods of from one to three months, when they are able to discard it.

A profound drop of blood pressure after the second stage may lead to problems of reduced cerebral and coronary circulation in patients who have already had a cerebral or coronary thrombosis and requires extra efforts to maintain a higher blood pressure the first two days after operation. Our main reliance is on a constant flow of 1 per cent solution of neosynephrin in 5 per cent glucose and maintenance of shock position.† Another rare

* The corset and G-suit are supplied by the Spencer Corset Company, to whom we are also indebted for the photographs.

† A note of warning is appended; two efforts to maintain a higher blood pressure level by pneumatic leggings led to temporary ischemic paralysis and foot drop when the systolic blood pressure fell to 80 mm., the level of air pressure found necessary to keep the suit inflated to raise the blood pressure 10 mm.

undesirable effect of this type of operation has been the appearance of Raynaud's phenomenon in the fingers of three patients. Palmer [4] has also reported such occurrences.

The prolonged and often extremely uncomfortable convalescence now makes us ask, "Is this patient's hypertension producing, or is it likely soon to produce, enough cardiovascular renal degeneration to justify such a serious operation? In the second place, are the changes already present irreversible?"

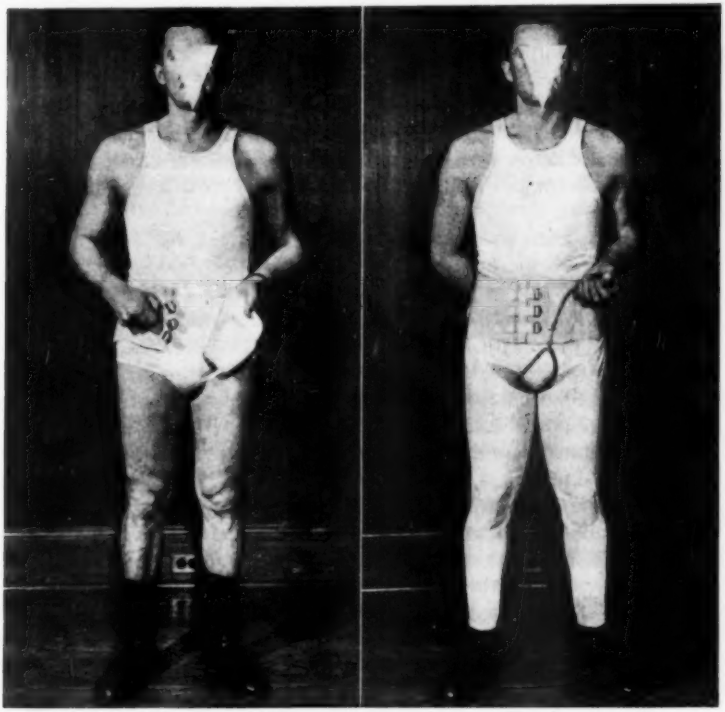


FIG. 6. FIG. 7.

FIG. 6. Girdle with suprapubic spring pad worn for orthostatic hypotension after high dorsolumbar sympathectomy (Spencer Corset Company).

FIG. 7. Pneumatic leggings worn for severe hypotension following high dorsolumbar sympathectomy (Spencer Corset Company).

CRITERIA FOR HIGH DORSOLUMBAR SYMPATHECTOMY

Our criteria for selection of patients, since adopting the almost complete sympathectomy has, therefore, drastically changed in the past three years, and the purpose of this review is to determine whether results have justified operating on patients with more advanced hypertensive vascular disease.

Two courses were open to us: to operate on all patients with hypertension except the almost moribund, or to put a ceiling on our indications. Former experience during our period of gradually raising the level of sympathectomy and the reports of others in the field—Smithwick,[5] de Takats,[6] operating to levels as high as the ninth thoracic ganglion and Grimson [7] with a complete sympathectomy—made us choose the latter course. This policy has led us to set up a negative set of standards or certain criteria which if present would contraindicate operative procedures.

Parenthetically, the Wagener-Keith classification [8] of hypertension which we have used in previous reports from this clinic and are using again for the sake of comparison, may be reviewed.

Group I. Patients whose blood pressure drops to normal on rest with Grade I fundi, the earmark of which is increased light reflex only.

Group II. Patients whose blood pressure drops to normal or near normal on rest or sedation with sodium amytal. Fundi are Grade II, the earmark of which is compression at the arteriovenous crossings and often some spasm.

Group III. Patients whose blood pressure drops but little on rest or sedation; fundi, earmark of which is hemorrhage or exudate often with marked spasm.

Group IV. Patients with high blood pressure which does not drop on bed rest or sedation with sodium amytal. In the latter test, the diastolic pressure stays well above 100. Fundi are Grade IV, the earmark of which is choked disk or edema of the disk. There is also hemorrhage, exudate and fragmentation of the vessels.

It must be stated here that many patients with Grade III or IV fundi may have labile blood pressures, that is, the diastolic pressure will still drop below 100 mm. of mercury on sedation with sodium amytal or will drop after etamon to below 100 mm. in the supine position (etamon will cause an orthostatic hypotension in almost all patients with any grade of hypertension and by experience such an orthostatic hypotension indicates nothing).

Our cases are tabulated according to Wagener and Keith's classification based on fundi alone for the sake of simplification, and because earlier reports from this clinic have also been on this basis. Although Wagener and Keith required certain degrees of lability of blood pressure in order to classify cases in each of their four groups, practically, it is impossible to do so because a patient with Group IV fundi may have Group I lability. A reclassification, therefore, along the lines suggested by de Takats,[6] taking into account lability, vascular and visceral damage, would seem more practical and satisfactory since results from all types of sympathectomy fall in line better with such a regrouping. For instance, a patient with Grade III or occasionally even Grade IV fundi may have a good result if the blood pressure is still labile, and renal, cardiac and vascular damage is still moderate. All 10 of de Takats' patients in Group III died, nine within one year, whereas many patients with Grade III fundi have good results.

What we have termed our negative criteria for operation are as follows:

(1) We rarely operate immediately on patients with Grade I fundi and with blood pressures that fall to normal on rest in patients of any age. We prefer to follow their course for a few years and attempt psychotherapy in the neuropsychiatric department, in most of the young patients. We believe that many of these patients have benign hypertension and will tolerate their labile blood pressure well for a normal life span. If under observation their basal resting diastolic pressure is consistently found to be above 100 mm. or signs of vascular or cardiorenal damage develop, we advise operation.

(2) We rarely accept patients over 50 years of age but have operated upon a few between 50 and 57 years of age if they still had a labile blood pressure, did not show evidence of arteriosclerosis or did not have Grade IV fundi. By labile blood pressure we mean a diastolic pressure that will fall below 100 mm. of mercury after administration of sodium amytal and below 100 mm. in the supine position after giving 3 c.c. of etamon intravenously. Our search for arteriosclerosis includes roentgenograms for calcification of the cerebral arteries as well as evidence of calcification in the aortic arch in the routine seven foot chest plate, of the pelvic arteries in the intravenous pyelogram, and often a roentgenogram with soft technic for the arteries in the leg. The presence of arcus senilis and palpably hardened peripheral arteries is included in the vascular survey.

(3) We reject patients with long-standing hypertension who have reached the age of 50 and who seem to be tolerating their hypertension well; in other words, their renal function is still good, their hearts are not enlarged and they have only Grade I or II fundi. These patients probably will live as long without operation as with it.

(4) Patients are refused surgery who have marked hemiplegic residual symptoms in whom operation would hardly be worth while on account of marked hemiplegic crippling effect. Minor cerebrovascular accidents from which the patient has largely recovered do not by themselves contraindicate operation.

(5) No patient is accepted who has severe right side congestive failure, but those who have experienced episodes of nocturnal dyspnea (pure left ventricular failure) are not considered to have a contraindication if renal function is good and the blood pressure labile.

(6) We reject patients who have any severe degree of coronary insufficiency or who have had coronary infarction. The existence of mild angina pectoris with normal exercise tolerance tests, a normal sized heart, and without much dyspnea on exertion, or angina pectoris with a large neurogenic factor does not contraindicate operation. Indeed, a patient with such findings is now subjected to a sympathectomy to the stellate ganglion level to include the anginal pathway.

(7) We do not accept patients with poor renal function, especially if the nonprotein nitrogen remains over 40 mg. per 100 c.c. or if the intravenous

pyelogram shows inadequate concentration of the dye. Poor concentration on the Fishberg test, poor phenolsulfonphthalein excretion, albumin in the urine, poor urea clearance, and a few casts or red blood cells in the urine should not individually rule out a candidate. A combination of such poor tests, however, points to such renal damage that it may be considered irreversible and the patient rejected for operation.

(8) We carefully screen out the following: glomerulonephritis, coarctation of the aorta, polycystic kidneys, pheochromocytoma, brain tumors, endocrine disease such as Cushing's syndrome, the systolic hypertension of arteriosclerosis and patients with unilateral Goldblatt's kidney. In the case of Goldblatt's kidney it has been our policy to do a splanchnicectomy on the same side as we do a nephrectomy. We then wait to see whether there is a secondary rise of blood pressure after this first stage splanchnicectomy. If there is, splanchnicectomy on the other side is carried out. If there is not a rise of the blood pressure after the first stage splanchnicectomy, we attribute the hypertension to the Goldblatt's kidney and do not complete the splanchnicectomy.

(9) Finally, we reject the patient with Grade IV fundi if he has a fixed blood pressure with or without the usual widespread cerebrocardiorenal disease.

The positive indications for operation are:

(1) We urge operation on patients with Group II fundi and labile blood pressure, believing that we get good results in 73 per cent. We especially recommend operation if there are signs of degenerative cardiovascular or renal disease which we believe are still reversible. This may include individuals with an enlarged heart but without a history of congestive failure. If there is evidence only of early renal sclerosis with albumin in the urine, some limitation of concentration function and nocturia, they are accepted for operation. Albumin and nocturia will often disappear after splanchnicectomy. In this group, too, we believe that spasm and compression in the fundi constitute a positive indication for operation rather than a contraindication, providing the blood pressure is still labile and there is no advanced arteriosclerosis.

(2) We operate on many patients with Group III or IV fundi if there is a fair degree of lability of blood pressure and none of the cardiovascular renal contraindications stated under "negative criteria." We inform the patient and family that if he does not have an operation, the four-year survival rate is 20 per cent. If he is operated on, the four-year survival rate may be 50 per cent. Do they want to take a chance with nature or with surgery? If the family understands the situation, operation is performed. Of course, it is in this group that the operation earns ill repute. We cannot deny splanchnicectomy to the 36 per cent of these patients who will have good results plus 41 per cent of patients who will have fair results.

(3) We also include patients for operation who have chronic pyelonephritis with hypertension whose nonprotein nitrogen is not elevated and whose intravenous pyelograms still show fair power of concentration. An added requirement for the treatment of chronic pyelonephritis is to sterilize the patient's urine before operation.

Results

The results tabulated are for a follow-up period of six to 33 months, average 11 months. In computing our results we have compared in table 1 the patient's first "off-the-street" blood pressure reading with an "off-the-street" supine blood pressure reading after operation at the last follow-up visit. To rank the result on supine blood pressure as excellent we have required a normal blood pressure. To rate the result as good, there must have been a fall of 50 mm. systolic and 20 mm. diastolic, and the blood pressure must have fallen below 200 mm. systolic and 120 mm. diastolic. To rank the result as fair, the systolic must have dropped 30 mm. and the diastolic 10 mm., but the blood pressure is above 150 mm. systolic and 100 mm. diastolic. The blood pressure drops of 10 patients who died several months after operation are included in these tables on supine and standing blood pressure.

Table I

Results of High Dorsolumbar Sympathectomy on Supine Blood Pressure

	Group I	Group II	Group III	Group IV	Total
Excellent	3	31	5	0	39
Good	3	29	9	1	42
Fair	1	19	11	2	33
Poor	1	32	20	6	59
Total	8	111	45	9	173

Summary of Results on Supine Blood Pressure

	Groups I and II	Group III	Group IV	Total
Excellent or good	55.5%	31.0%	11.0%	46.8%
Fair	16.8%	24.5%	22.2%	19.0%
Poor	27.7%	44.4%	66.6%	34.1%

We have also compared the "off-the-street" blood pressure of the patient's first visit with the standing blood pressure of the final follow-up visit (table 2). This comparison, naturally, yields the most impressive results. We have been especially interested in the marked orthostatic hypotension produced by this extensive operation since it is believed to cause a redistribution of circulating blood volume responsible for the relief of symptoms and cardio-

vascular improvement. If the patients live longer following splanchnicectomy it is probably because such an orthostatic hypotension has been brought about. Furthermore, the high supine blood pressure recorded in the physician's office may not be that of the patient when he is asleep supine. In other words, the average blood pressure the clock around is bound to be much lower in the patients who have obtained a good orthostatic hypotensive result.

TABLE II

Results of High Dorsolumbar Sympathectomy on Orthostatic Blood Pressure

	Group I	Group II	Group III	Group IV	Total
Excellent	6	62	15	2	85
Good	0	14	7	1	22
Fair	2	23	11	2	38
Poor	0	10*	10	4	24
No report		2	2		4
Total	8	111	45	9	173

* 1 operative death.

Summary of Results on Orthostatic Blood Pressure

	Groups I and II	Group III	Group IV	Total
Excellent or good	69.0%	48.8%	33.3%	62.0%
Fair	21.0%	24.4%	22.2%	22.0%
Poor	8.4%	22.2%	44.4%	13.8%
No report	1.0%	4.4%		2.3%

In the table for orthostatic effect on blood pressure after sympathectomy, excellent means a blood pressure after one minute or more in the standing position, not exceeding 150 mm. systolic and 100 mm. diastolic; good means an orthostatic blood pressure above 150 mm. systolic and 100 mm. diastolic, with a marked drop compared with the "off-the-street" blood pressure before operation. For a fair rating there has been only a moderate drop in blood pressure but a standing pressure below 200 mm. systolic and 120 mm. diastolic. A rank of poor means the standing blood pressure is still above 200 mm. systolic and 120 mm. diastolic, or with no or very little drop (table 2).

COMMENT ON RESULTS ON SUPINE AND ORTHOSTATIC BLOOD PRESSURE

From a review of tables 1 and 2 it is apparent how frequently a good orthostatic drop in blood pressure is obtained and how disappointing the effect on the supine blood pressure may remain. Only 34 out of 119 patients with

Groups I and II fundi had normal postoperative blood pressure when lying down, but 68, or more than one half, had normal blood pressures when standing up. Only one-ninth of the patients with Group III fundi had normal supine blood pressures following operation, but one-third had a normal blood pressure when erect. About a fourth of patients with Groups I and II fundi had poor results on supine blood pressure, but only 8.4 per cent had a poor result on their erect blood pressure. In Group III, 44 per cent of the patients had poor results on supine blood pressure and 22 per cent when the patient was standing. Of the entire series of 169 patients, on whom there is a report on the standing blood pressure, only 24 or 14 per cent failed to obtain at least a moderate drop of their blood pressure when they were erect.

Symptomatic Improvement, Economic Status and "Total Score"

In arranging our statistical tables for symptoms and economic status (tables 3, 4 and 5) we tried to avoid the old cliché that one can prove anything by statistics and looked at the results from the viewpoint of both the patient and his referring physician. Our criteria for scoring in tables 3, 4 and 5 are as follows:

Table III

Relief of Symptoms after High Dorsolumbar Sympathectomy

	Group I	Group II	Group III	Group IV	Total
Excellent	0	9	1	0	10
Good	5	69	25	1	100
Fair	3	14	11	2	30
Poor	0	6*	4*	6*	16†
No report		13	4		17
Total	8	111	45	9	173

* 4 deaths.
† 12 deaths.

Summary of Results on Symptoms

	Groups I and II	Group III	Group IV	Total
Excellent or good	69.7%*	57.7%*	11.1%	63.5%
Fair	14.3%	24.4%	22.2%	17.3%
Poor	5.0%†	8.9%†	66.6%†*	9.2‡
No report	11.0%	8.9%		9.9%
Total	100%	99.9%	99.9%	99.9%

* 78% of those patients reporting.
† 4 deaths.
‡ 12 deaths.

TABLE IV

Economic Status after High Dorsolumbar Sympathectomy

	Group I	Group II	Group III	Group IV	Total
Excellent (100% at 3 mos.)	1	17	2	0	20
Good (100% at 6 mos.)	1	40	14	1	56
Fair (75% at 6 mos.; 100% at 1 yr.)	2	16	5	2	25
Poor (not working)	1	4*	8*	6*	19**
No report	3	34	16		53
Total	8	111	45	9	173

* 4 deaths.
** 12 deaths.

Summary of Economic Status

	Groups I and II	Group III	Group IV	Total
Excellent or good	49.5%	35.5%	11.1%	44.0%
Fair	15.1%	11.1%	22.2%	14.4%
Poor	4.2%	17.7%	66.6%	11.0%
No report	31.1%	35.5%		30.6%

TABLE V

Total Score

	Group I	Group II	Group III	Group IV	Total
Excellent	0	4	0	0	4
Good	7	77	20	1	105
Fair	1	19	19	3	42
Poor	0	8	6	5	19
Insufficient data		3			3
Total	8	111	45	9	173

Summary of Total Score

	Groups I and II	Group III	Group IV	Total
Excellent or good	74.0%	44.4%	11.1%	63.0%
Fair	16.8%	42.2%	33.3%	24.2%
Poor	6.7%	13.3%	55.5%	11.0%
Insufficient data	2.5%			1.7%

Under symptoms, complete relief counted a score of excellent. Good means relief of all but one of the following symptoms: nervous tension, headache, dizziness, fatigue, plus a sense of well-being. Fair represents partial relief of all or most symptoms, or partial return of some symptom, usually headache. The 12 deaths in the entire series were counted poor as regards symptoms and economic status. Economic improvement is explained in the table.

The "total score" (table 5) was computed as follows: excellent in any of the categories counts four points toward a total of 16; good counts 3; fair counts 2; poor 1; no report 0. The count of 1 for poor was compensated for by raising the total requirements 1 point for each final category in the "total score."

A score of excellent in the "total score" requires 15 to 16 points; good 10 to 14 points; fair 7 to 9 points; any score below 7 rates poor. The 12 fatalities are rated poor. Thus one patient in Group III who had a good result in all four categories for a total score of 12, died from a sudden cerebral accident nine months after operation, but must naturally be counted a poor result.

Comment on Symptomatic Improvement, Economic Status and "Total Score"

Seventy-eight per cent of patients in Groups I and II and 63 per cent in Group III who reported symptoms on follow-up examination obtained marked relief, but in Group IV two-thirds of the patients failed to obtain relief or died (table 3).

Seventy-two per cent of patients reporting in Groups I and II were working full time six months after operation, 94 per cent by one year (table 4). Fifty-five per cent of patients reporting in Group III were working full time six months after operation, 74 per cent by one year. Eighty-four per cent of those reporting in the entire series were working full time by one year.

The good "total score" in Grades I and II (table 5) exceeds the good orthostatic blood pressure result by only 5 per cent, 74 per cent and 69 per cent, respectively. Only 29.1 per cent of patients in these two groups failed to obtain a good orthostatic fall of blood pressure. In patients with Group III fundi the good "total score" and good fall of orthostatic blood pressure were again parallel, 44.4 per cent and 48.8 per cent, respectively, and failure to get a good fall was 46.6 per cent. If one adds the percentage for total excellent and good score to the percentage of failure to get a good orthostatic drop in blood pressure, almost exactly 100 per cent of the patients are accounted for in Groups I, II and III. This substantiates our belief that the chief benefit of this operation is the redistribution of circulating blood volume.

Only 11 per cent of good results (table 5) in patients with Group IV fundi, and over one half poor results emphasize the importance of this contraindication to operation.

The results for 15 patients with Group II fundi would be raised from good to excellent on their total score if they had been able to resume full time work in three months instead of six. We have kept this strict criterion because it reflects the long convalescent period from this type of operation.

Effect of Operation on Vascular Areas

While decrease in blood pressure is certainly a desirable result, we doubt that it should be considered the only judge of the benefit of splanchnicectomy since even more startling benefits are often observed even when the fall in blood pressure has not always been satisfactory. Therefore, we have prepared tables showing improvement in areas of cardiovascular degeneration. Bridges et al.[9] have reported similar improvement in cardiac findings following dorsolumbar sympathectomy.

1. Cerebral Vascular Area. We believe with de Takats[6] and Smithwick[3] that the symptomatic and visceral improvement is due to redistribution of circulating blood with lowering of venous pressure and diminished diastolic cardiac filling, the effect of orthostatic hypotension. Previous experience before this series now reported, had taught us that if cardiac reserve has been too limited before operation, diminished diastolic filling may only tax the heart further and give rise to serious symptoms of forward failure. Reduced coronary irrigation may result in angina of serious coronary insufficiency. On the other hand, we have not observed any ill effects from reduced cerebral irrigation except immediately after operation, after both the first and second stages (table 6). There were two deaths in this series soon after operation from this cause, both in patients who had had no previous cerebrovascular accident.

Table VI

Cerebrovascular Accidents

	Preoperatively	Postoperatively
Group I	1	0
	0 in 7	0
Group II	9	1
	0 in 101	4 (2 fatal at op.)
Group III	9	0
	0 in 33	3 (2 fatal)
Group IV	1	0
	0 in 7	1 (fatal)

Twenty patients had had cerebrovascular accidents prior to surgery, only one of whom had a subsequent nonfatal stroke. Of patients who never had had similar troubles, there were eight cerebrovascular accidents, varying in time from a few days to several months after operation, two of which were fatal. It would seem a previous cerebrovascular accident need not deter us from operating.

2. Cardiac Vascular Area. A. Angina (table 7). Nine of 15 patients with angina experienced abolition of pain and two partial relief. Angina remained the same in one, became worse in two, one of these patients dying of coronary infarction. Since one-third of our patients with angina did not

obtain complete relief, we feel supported in our present practice of resecting bilaterally the anginal pathway of the first, second, third and fourth thoracic ganglions. We did not operate on any patient with an electrocardiographic pattern of coronary infarct.

TABLE VII
Angina

Group I				Group II				Group III				Group IV			
Before	After	Left	Right	Before	After	Left	Right	Before	After	Left	Right	Before	After	Left	Right
+	0	T-4	T-5	+	0	T-4	T-5	+	0	T-4	T-4	+	0	T-4	T-4
				+	++*	T-4	T-5*	++	+	T-4	T-4				
				0	+	T-4	T-4	+	+	T-4	T-4				
				+	0	T-4	T-4								
				++	0	T-5	T-4†								
				+	0	T-3	T-5								
				+	0	T-4	T-4								
				++	+	T-4	T-4								
				0	+	T-3	T-5								
				+	0	T-2	Stellate								

* Died of coronary infarction 12 months after operation.
† Died of auricular fibrillation 16 months after operation.

In the last series of cases reported from the Lahey Clinic by Poppen [2] there were eight patients with angina, in none of whom was resection carried to the fourth thoracic level. Only one patient obtained complete relief, two patients were better as regards angina, and five subsequently died. When operation was below the fourth thoracic level, there was 12.5 per cent relief; at the fourth thoracic level, 60.0 per cent relief, one patient undergoing resection to the second thoracic ganglion on the left and to the stellate ganglion on the right. It will be interesting to note what the results on angina will be when more patients are subjected to the still higher operation.

B. Heart size (table 8; figure 8). The hearts of 51 patients were reported preoperatively to have a transverse cardiac diameter greater than 50 per cent of the greatest transverse diameter of the chest. Twenty of these revealed normal ratios, many as soon as three to six months after operation; in eight the heart was reduced in size, two showed no change and in one the

TABLE VIII
Change in Heart Size

	Cases
Enlarged before operation	51
Normal size 3 to 6 mos. after operation	20
Reduced but still enlarged	8
No change	2
Larger	1
Unreported	20

Reduction of size in 90%; 64% to normal

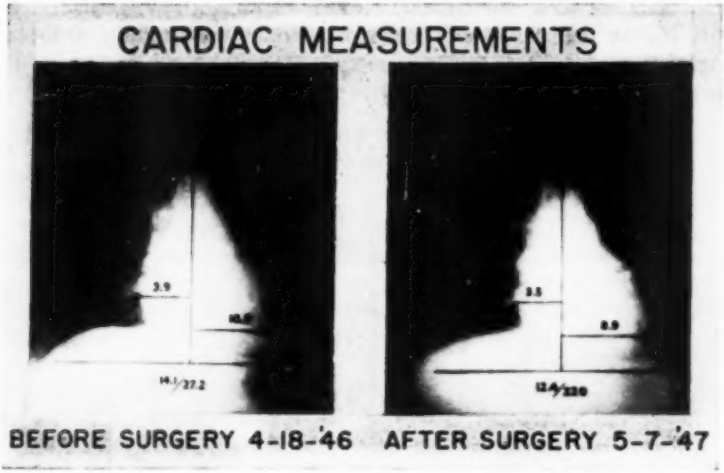


FIG. 8. Decrease in heart size to normal one year after sympathectomy.

heart was larger. There was no follow-up on heart size in 20 per cent. Of those with check-up examinations after operation, 90 per cent showed reduction in the transverse diameter of the heart, 64 per cent to normal.

C. Electrocardiogram (table 9; figure 9). Of a total of 173 patients the electrocardiograms were normal in 41 and abnormal in 92 before operation. Fifty of these latter patients had follow-up electrocardiograms after operation. Of these 50, 21 showed improvement (42 per cent), 28 no change and one was worse.

TABLE IX

Electrocardiographic Data

	Left Axis Deviation Only					Left Ventricular Strain				Normal		
	Total	Improved	Same	Worse	No Report	Total	Improved	Same	No Report	Total	Same	No Report
Group I	1				1					6	1	5
Group II	27	2	8		17	28	11	7	12	30	6	24
Group III	16	0	11	1	3	19	8	2	9	3		3
Group IV						1			1	2	2	

D. Aorta. Of 11 patients who had widened, tortuous or calcified aortas, five had a total score of good, three of fair and three poor, making eight patients in whom the operation may have been worth while. In a few of these patients the aorta was noted to be less tortuous after operation.

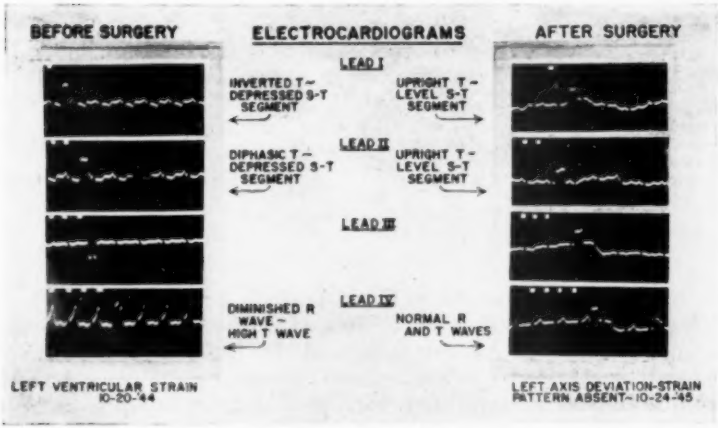


FIG. 9. Disappearance of left ventricular strain pattern one year after sympathectomy.

TABLE X

Renal Function

	Nocturia	Improvement	Same	Worse
Group II	21	14	6	1
Group III	21	17	3	1
Group IV	3	3		

	Impaired	Improved in 1 or More Tests	Same	Worse
Group II (adequate comparative tests before and after operation)	36	21	12	3
Group III (adequate comparative tests before and after operation)	16	8	6	2
Group IV	3	3		

3. Renal Area (table 10). A. Nocturia was a symptom in 45 of the entire series of 173 patients. There was complete or partial relief in 34, or 75 per cent. Nocturia remained the same in nine and became worse in two.

B. Impaired renal functional tests were found in 55. After operation there was improvement in one or more tests in 32, or 58 per cent. The tests were practically the same in 18 and worse in 5. The tests included in this summary were for albumin, casts, Fishberg concentration tests, and often a phenolsulfonphthalein excretion and urea clearance test.

4. Fundi (table 11). A follow-up examination of the fundi was recorded in 117 patients in Grades II, III and IV. All fundi were graded by the senior author (J. A. E.). There was a reversion to normal in 12, in one of whom the fundi were originally Grade III. Thirty-seven of 73 who

TABLE XI
Fundi

	Group II	Group III	Group IV
Reverted to I	37	6	2
Reverted to II		29	3
Reverted to III			1
Reverted to normal	11	1	
No change	25	2	
Advanced	0	0	0
Total	73	38	6

had Grade II fundi improved to Grade I, 25 showed no change; 38 with Grade III fundi were checked and 29 changed to II, six to I and there was no change in two. Of six patients with Grade IV fundi, one changed to III, three to II and two to I. It is to be noted that all Grade IV fundi improved. Two patients who were practically blind were able to read again one to two months following operation. No ocular fundi became worse after operation, although with the passage of time some Grade III fundi which improved for a while reverted to Grade III. These are included under no change.

ANALYSIS OF DEATHS

There were 12 deaths in the entire series of 173 patients, a mortality of 7 per cent within a six to 33 month follow-up period. Two fatalities occurred before the patients had left the hospital, giving an operative mortality of 0.5 per cent (two operations were carried out on each patient). Both these figures are the same as in Poppen's last series of lower resections. Ten patients died five to eighteen months after operation, two of these 10 from coronary occlusion, three of cerebrovascular accident, and three of uremia. The cause of death is unknown in two (table 12).

TABLE XII
Analysis of Deaths

	Total Deaths	Operative Mortality	Case Mortality			
		Cerebrovascular Accident	Coronary	Cerebrovascular Accident	Uremia	Cause Unknown
Group I	0	0				
Group II	4	1	2{18 mos., 15 mos.			13 mos.
Group III	4	0		2{11 mos., 10 mos.	7 mos.	12 mos.
Group IV	4	1		14 mos.	2{7 mos., 5 mos.	
Total	12					

Operative mortality, 0.5%.
Mortality, 7%.

General Comments

Psychic relief has been a striking result in 60 per cent and fair in an additional 20 per cent of patients reporting release in varying degrees from nervous tension. Patients often volunteer such remarks as, "Things don't bother me like they used to," "Now I can sit and relax and not have to get up and go out." Whether this effect is psychologic or from cutting psychosomatic pathways is conjectural.

The average age of poor total score in patients with Groups II and III fundi was 42.5 years, of fair results was 41.1 years and of good results, 41.7 years. Therefore, in 156 patients none of whom were over 55 years, age seems to make no difference in results. This agrees with a statement by de Takats.[10] Patients with Group IV fundi have been left out of this consideration because malignant hypertensives average younger, yet have the poorest results.

It must be our next task to analyze our poor results and our best results in an attempt to reclassify our criteria for operation but we still believe it is too early to do so accurately since at least 100 patients with three-year follow-up studies are needed for a reliable opinion. High dorsolumbar or almost complete sympathectomy must justify itself on greater permanence of results since our main arguments for this operation are to resect a higher somatic sympathetic distribution and to prevent regeneration of the splanchnic nerves by creating a longer bed of scar tissue through which they must regrow.

In the category of patients with Group II fundi, Poppen in his series of

Table XIII

Comparison of Results of Last Reported Series of Cases from the Lahey Clinic with Resections to Various Levels Ranging from the Eleventh to the Fourth Thoracic Ganglions and the Present Series All to the Fourth Thoracic Level*

	Groups I and II	Group III	Group IV
Good			
First series	39.0%	21.0%	4.0%
Second series	74.0%	44.4%	11.1%
Fair			
First series	16.0%	8.0%	0.0%
Second series	16.8%	42.2%	33.3%
Poor			
First series	23.0%	37.0%	56.0%
Second series	9.2%	13.3%	55.5%

Summary of All Groups in Both Series

	First Series	Second Series
Good	47.0%	63.0%
Fair	24.0%	24.2%
Poor	22.0%	12.7%

* Comparison is somewhat misleading because the earlier group was followed for one to four years, while the present group has been followed for only six months to three years.

lower operation reported from this clinic 23 per cent unsatisfactory results (table 13). We now report 6.7 per cent unsatisfactory on the basis of "total score," 9.2 per cent when cases with insufficient data are included, 8.4 per cent unsatisfactory from the viewpoint of erect blood pressure and 27.7 per cent unsatisfactory for supine blood pressure.

We regard the group of hypertensive patients with Grade III fundi as the real testing ground for high dorsolumbar sympathectomy, having designed the operation in the hope of better meeting their need than lower sympathetic resection had proved to do in our hands. With the lower operations on patients with Group III fundi, this clinic had 37 per cent unsatisfactory results; with the high resection to the fourth thoracic level, 13.3 per cent (table 13). The good results in this critical group in the earlier series were 21 per cent, in the present series 44.4 per cent based on "total score." We can only hope longevity figures 10 years from now will justify our expectation that we are salvaging a larger number of patients with severe hypertension by high dorsolumbar sympathectomy.

The evaluation of high dorsolumbar sympathectomy must await the test of time. Will taking the higher ganglions prevent regeneration of the splanchnic bed? It is also our belief that many patients will go on having sclerosing arteriolar disease whether or not there is regeneration of their splanchnic nerves. Other patients will continue to produce more and more pressor substance and many others will continue to be hyperkinetic, and slowly redevelop even orthostatic hypertension.

Summary and Conclusions

This study of the results of high dorsolumbar sympathectomy from the fourth thoracic to the second or third lumbar ganglions, was undertaken in an attempt to ascertain whether a larger number of patients with all types of hypertension were being aided than by lower sympathetic resection in former series reported from this clinic. Special interest has been taken to determine whether more patients with Group III fundi (Keith-Wagener) may be salvaged. All the operations have been performed by one surgeon, Dr. James L. Poppen, except a very few recently by his associate, Dr. Kenneth E. Livingston. Although the present series has been followed a shorter time and doubtless with the passage of one or two more years the difference in figures will not be so marked (table 13), the superiority of results in patients with Group III fundi (hemorrhage and exudate) has doubled, from 21 to 44 per cent. Poor results have dropped one-third, from 37 to 13 per cent.

Good results in patients with Groups I and II fundi have almost doubled, from 39 to 74 per cent, and poor results are less than one half, having dropped from 23 to 9 per cent.

The principal effect of splanchnicectomy on hypertension is orthostatic, and evidence is reported that symptomatic relief is parallel to drop in orthostatic rather than supine blood pressure.

High dorsolumbar sympathectomy did not protect eight patients among the 173 in this series from subsequent cerebrovascular accident, two of them fatal.

Angina was wholly or partially relieved in 60 per cent of 15 patients, none of whom had serious coronary disease.

Ninety per cent of patients with abnormally wide transverse diameters of the heart showed reduction of heart size, 64 per cent to normal.

There was improvement in 42 per cent of 50 patients who had abnormal electrocardiograms.

Seventy-five per cent of 45 patients with nocturia reported complete or partial relief. At least one renal function test was improved in 58 per cent of 55 patients who had one or more impaired tests before operation.

Retinal vascular change improved in 66 per cent of 117 patients on whom follow-up examination was possible.

Operative mortality was 0.5 per cent; mortality rate for the entire series within the follow-up period of six to 33 months was 7 per cent.

We are loathe to consider this type of operation with its prolonged uncomfortable convalescence as a prophylactic operation for benign hypertension but urge it on patients under 50 years of age with spastic, exudative and hemorrhagic retinal arteriolar changes, moderate cardiac damage, signs of early nephrosclerosis, and labile blood pressure.

BIBLIOGRAPHY

1. Bartels, E. C., Poppen, J. L., and Richards, R. L.: Surgical treatment of hypertension (results in 52 cases), Ann. Int. Md., 1942, xvii, 807–811.
2. Poppen, J. L., and Lemmon, C.: The surgical treatment of essential hypertension, Jr. Am. Med. Assoc., 1947, cxxxiv, 1–9.
3. Freis, E. D., and Smithwick, R. H.: The effect of lumbodorsal splanchnicectomy on the blood volume and thiocyanate space of patients with essential hypertension, Am. Jr. Med. Sci., 1947, ccxiv, 363–367.
4. Palmer, R. S.: Medical evaluation of the surgical treatment of hypertension, Jr. Am. Med. Assoc., 1947, cxxxiv, 9–14.
5. Smithwick, R. H.: The surgical treatment of continued hypertension; some suggestions about selection of cases for this form of therapy, Jr. Med. Soc. New Jersey, 1947, xliv, 304–316.
6. de Takats, G.: Technique for splanchnic resection for hypertension; preliminary report, Surgery, 1940, vii, 1–8.
   de Takats, G., Graupner, G. W., Fowler, E. F., and Jensik, R. J.: Surgical approach to hypertension. Second report, Arch. Surg., 1946, liii, 111–163.
7. Grimson, K. S.: Total thoracic and partial to total lumbar sympathectomy and celiac ganglionectomy in treatment of hypertension, Ann. Surg., 1941, cxiv, 753–755.
8. Keith, N. M., Wagener, H. P., and Barker, N. W.: Some different types of essential hypertension; their course and prognosis, Am. Jr. Med. Sci., 1939, cxcvii, 332–343.
9. Bridges, W. C., Johnson, A. L., Smithwick, R. H., and White, P. D.: Electrocardiography in hypertension (study of patients subjected to lumbodorsal sympathectomy), Jr. Am. Med. Assoc., 1946, cxxxi, 1476–1480.
10. de Takats, G., Fowler, E. F., Jordan, P., and Risley, T. C.: Sympathectomy in the treatment of peripheral vascular sclerosis, Jr. Am. Med. Assoc., 1946, cxxxi, 495–499.
    de Takats, G., and Evoy, M. H.: Sympathectomy for peripheral vascular sclerosis, Jr. Am. Med. Assoc., 1947, cxxxiii, 441–445.

RETROGRADE ARTERIOGRAPHY IN THE DIAGNOSIS OF CARDIOVASCULAR LESIONS. I. VISUALIZATION OF ANEURYSMS AND PERIPHERAL ARTERIES *

By NORMAN E. FREEMAN, M.D., and EARL R. MILLER, M.D.,
San Francisco, California

RECENT advances in vascular surgery have created a demand for more accurate methods of diagnosis. Just as developments in surgery of the abdomen, urinary tract, head, and thorax have been aided by improvements in radiographic technic, so advances in vascular surgery may be expected to develop with visualization of the heart and blood vessels after the injection of contrast media. The present paper is presented to show the development of our use of retrograde arteriography in the visualization of lesions of the aorta and of peripheral vessels.

Sicard and Forestier [1] were the first to visualize the blood vessels of the human extremity through injection of radio-opaque material. Their work in France was followed in the same year by that of Berberich and Hirsch [2] in Germany and by Brooks [3] in this country. The contributions of Dos Santos [4] established the usefulness of angiography as a diagnostic method. Injections are usually made into the blood vessel in the direction of the blood flow; toward the heart for visualization of veins and toward the periphery in the arteries. Visualization of the abdominal aorta by direct puncture below the twelfth rib was first described by Dos Santos [4] and has been extensively used by Nelson,[5] Doss,[6] and Wagner.[7] Radiography of the thoracic aorta was accomplished by Blakemore [8] by means of a needle inserted directly into this structure. More recently Hoyos and Del Campo [9] have described a method for the introduction of 30 c.c. of 70 per cent Diodrast directly into the aorta by way of an 18 gauge needle, in order to visualize the thoracic aorta and coronary vessels.

Farinas [10] in his attempts at abdominal aortography discarded the technic originally suggested by Dos Santos of inserting a needle directly into the lower thoracic aorta through the intact skin, in favor of a retrograde method. He first used a catheter passed up through one of the femoral arteries.

Our first retrograde arteriogram was performed in the following patient by means of the catheter technic described by Farinas.

Case 1. This patient, a man of 56, was admitted for the first time to the University of California Hospital in November, 1940, with a diagnosis of bleeding duodenal ulcer. He had had abdominal distress related to meals for approximately 10

* Presented at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 23, 1948.

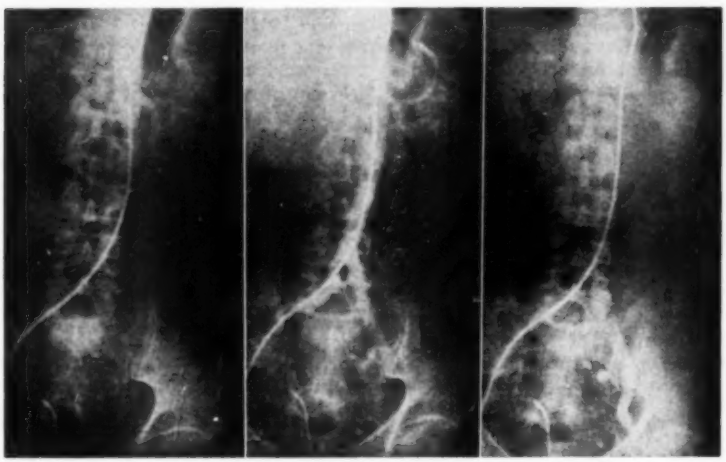
From the Divisions of Surgery and Radiology, University of California Medical School, San Francisco, California.

years and three days before admission had suddenly vomited a small amount of blood. He passed tarry stools for the next three days. He had been on a bland diet and in 1930 a gastrointestinal series had demonstrated the crater of an old ulcer. At the time of his admission in 1940 roentgen-ray examination showed an ulcer on the lesser curvature as well as a deformity of the duodenum, suggesting a second ulcer. He recovered uneventfully and was discharged on a bland diet without medication. He was well for two years until in 1942 he noted a tarry stool. Upon readmission his blood pressure was found to be 170 mm. Hg systolic and 115 mm. diastolic. Roentgen-ray examination revealed an ulcer on the bulb of the duodenum and also a small esophageal diverticulum with a questionable ulcer on the lesser curvature of the stomach. At exploratory laparotomy in March of 1942 a mass was discovered behind the stomach just above the pancreas, anterior and attached to the aorta. This mass was spherical, about 7 centimeters in diameter, quite firm and rubbery with an expansile pulsation. Aspiration failed to yield any fluid. A biopsy was performed, ¼ inch of the superficial portion of the lesion being removed. Microscopic examination revealed connective tissue compatible with the diagnosis of an aneurysm. Nothing further was done at the time of this operation. In August of 1942 he was again readmitted because of recurrent melena. There were no further difficulties until November, 1945. At that time he had a sudden onset of nausea, vomiting, and abdominal pain together with melena. The abdominal pain was similar to the episodes of "ulcer discomfort" but much more severe. At this time examination revealed persistent abdominal tenderness and a considerable increase in the size of the upper abdominal tumor. In the succeeding year the abdominal mass became increasingly larger and the patient suffered repeated bouts of severe vomiting and abdominal pain. The possibility of a hemangioma of the liver was considered but the general impression was that he had an aneurysm of the abdominal aorta. He was readmitted to the hospital on September 27, 1946, for visualization of the abdominal aorta.

On October 2, 1946, an attempt was made to pass a catheter into the thoracic aorta by way of the left brachial artery. Through a transverse incision the brachial artery was exposed just below the profunda, and a No. 10 ureteral catheter was passed up this artery under fluoroscopic control. However, at the first portion of the subclavian artery, despite repeated manipulations, the catheter went up into the cervical region rather than down the subclavian into the aorta. Accordingly, the catheter was brought out to the second portion of this artery and 12 c.c. of 70 per cent Diodrast were injected as rapidly as possible. Films taken of the lower abdominal aorta failed to show any dye. The patient suffered a rather alarming reaction associated with tachycardia and a drop in blood pressure, suggesting that the dye had gone into the cerebral circulation possibly by way of the vertebral artery. The catheter was withdrawn and the opening in the brachial artery sutured but thrombosis occurred. Good collateral circulation was present so that no ischemia of the hand developed although the radial pulse on the left side was only barely perceptible.

Because of persisting pain and the increasing size of the abdominal mass the patient was willing to have anything done which might give him relief. On October 15 a second attempt was made to visualize the abdominal aorta. Under local anesthesia, the right femoral artery was exposed just below the profunda. The artery was occluded with two artery clamps and a small transverse incision was made through which a short metal cannula was introduced. Through this cannula a No. 9 ureteral catheter was passed up into the femoral artery. Under fluoroscopic control the catheter could readily be passed up to the aortic arch. It was then withdrawn to a point just above the diaphragm. Twenty c.c. of 70 per cent Diodrast were injected within a period of three to four seconds and roentgen-ray films were taken

in rapid succession. Following withdrawal of the catheter the transverse incision in the superficial femoral artery was sutured but, upon release of the occluding arterial clamps, it was found that thrombosis had taken place above the operative site. Accordingly the common femoral artery was opened just above the profunda and a small thrombus was removed. The artery was irrigated with saline and heparin and the wound was sutured. Following release of the occluding arterial clamps, normal pulsation took place across the suture line and, at the conclusion of the operation, the ankle pulses were normal.



A B C

FIG. 1. Arteriogram of abdominal aorta obtained by injection of 70 per cent Diodrast through ureteral catheter inserted by way of right femoral artery.

As shown in figure 1 the upper abdominal aorta was well visualized in the first film and by the time the third film was taken both iliac vessels were well delineated. There was no filling of the mass with radio-opaque material and the aorta did not appear to be dilated and showed a smooth contour. It was accordingly decided that the abdominal aorta was probably not intrinsically diseased and that an attempt could be made to obliterate the aneurysm. Operation was performed on October 25. Through a transverse incision, the abdominal aorta was exposed from the bifurcation to the diaphragm by the retroperitoneal approach previously described.[11] With the aorta occluded above and below the mass, the peritoneum was opened. The aneurysmal sac was widely opened. Old laminated clot was removed and at the bottom two small openings were found which were closed with interrupted stitches of No. 40 cotton. The aneurysmal wall was not removed. The patient recovered and at the present time, 18 months since operation, is completely restored to health.

Comment: Retrograde arteriogram of the abdominal aorta in this patient disclosed a normal abdominal aorta and permitted restorative endoaneurysmorrhaphy.

Because of the complications which originated from retrograde arterio-

graphy with the catheter technic we decided to employ the retrograde injection method which Farinas had described in his second contribution.[12] According to this technic 70 per cent Diodrast is injected at 15 pounds pressure through a trocar 1.5 mm. in diameter. The injection is accomplished in two seconds. The next two patients in whom this retrograde technic was applied were patients with coarctation of the aorta but these cases will be reported elsewhere.

The patient is placed supine on a horizontal cassette tunnel; the long axis of the tunnel and the long axis of the roentgen-ray table on which it is placed run in the same direction. The tunnel is open on both of its longer sides and large enough to permit the easy passage of a 14 by 17 inch film cassette through it. A stationary grid is fastened to the top of the tunnel. A preliminary film is taken to check the position of the patient and technic, using a target film distance of 40 inches, 400 milliamperes, one-tenth to one-fifth of a second, and a voltage adjustment to give an exposure which adequately shows the thoracic spine detail.

After the preliminary film has been seen by the radiologist and any necessary corrections in technic made, the needle is inserted into the artery. The distal part of the artery is held shut and the injection is made as rapidly as possible. Seventy per cent Diodrast is the medium used. The dose is on the order of 1 c.c. per kilogram up to a maximum of 50 c.c.

It is imperative that the first film of the series be taken immediately on completion of the injection and the remaining two to three films as rapidly as the cassettes can be changed by hand (about every two seconds).

Retrograde arteriography of the abdominal aorta by retrograde injection of the contrast medium into the femoral artery has not been successful in our hands in four patients. In two of these patients a large abdominal aneurysm was present. In spite of the use of a 15 and a 16 gauge needle, with the injection of 30 to 40 c.c. of 35 per cent or 70 per cent Diodrast, adequate visualization of the abdominal aorta was not obtained. Similarly in two patients with the clinical diagnosis of thrombosed abdominal aorta visualization was not obtained.

Vascular lesions of the upper extremity have been more successfully shown. In the second case which we studied, the right subclavian artery was visualized by retrograde injection of the right common carotid artery.

Case 2. This patient was a 41 year old man who was admitted to the University of California Hospital in January, 1947, because of impaired circulation to the right hand of five months' duration. For two months prior to entry he had had severe attacks of Raynaud's phenomenon brought on by exposure to cold and associated with considerable pain. Roentgenograms taken a month before admission disclosed a cervical rib. At the time of admission physical examination revealed a mass above the right clavicle measuring 2 by 3 centimeters, absent pulses in the right upper extremity and atrophy of the muscles of the hand, forearm, and arm. There was no pulsation or bruit heard over the mass. The tip of the right index finger and thumb showed small areas of necrosis.

On January 25, under local anesthesia, the right common carotid artery was exposed and 20 c.c. of Thorotrast were injected in retrograde fashion. The first roentgen-ray film (figure 2) showed filling of the common carotid, innominate, and first portion of the subclavian artery with obstruction of the artery just beyond the thyro-

cervical axis. The collateral circulation was well visualized. The second film showed an irregular filling defect of the brachial artery at the profunda which suggested that there had been an embolic occlusion of this vessel. The patient was operated upon on January 30 and a thrombosed aneurysm of the third portion of the subclavian artery was discovered. The scalenus muscle was divided and a section of the aneurysm was removed. Following this operation there was abrupt relief of pain and a cessation of the attacks of Raynaud's phenomenon. Thirteen months after operation his hand was warm, there was no ulceration, and he was able to do full-time work. Oscillometry revealed a return of pulsation in the right forearm.

Comment: Retrograde arteriography was useful in this patient in visualizing the first and second portions of the right subclavian artery. This artery would have been difficult to inject by direct puncture. Visualization of the collateral circulation was of assistance at the time of operation.

Occasionally the location of the lesion may be such as to make it difficult to inject the contrast medium into the artery proximally. The following two examples are cited.

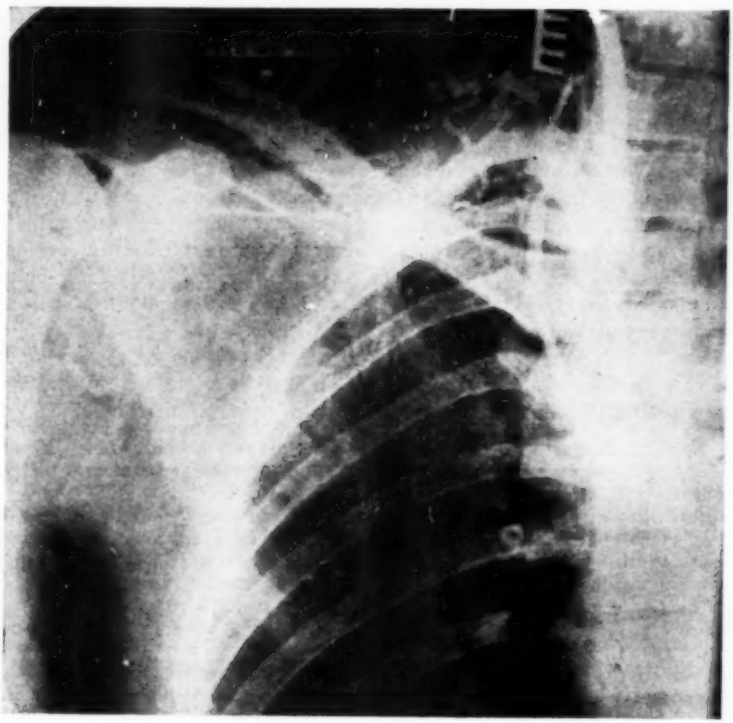


FIG. 2. A.

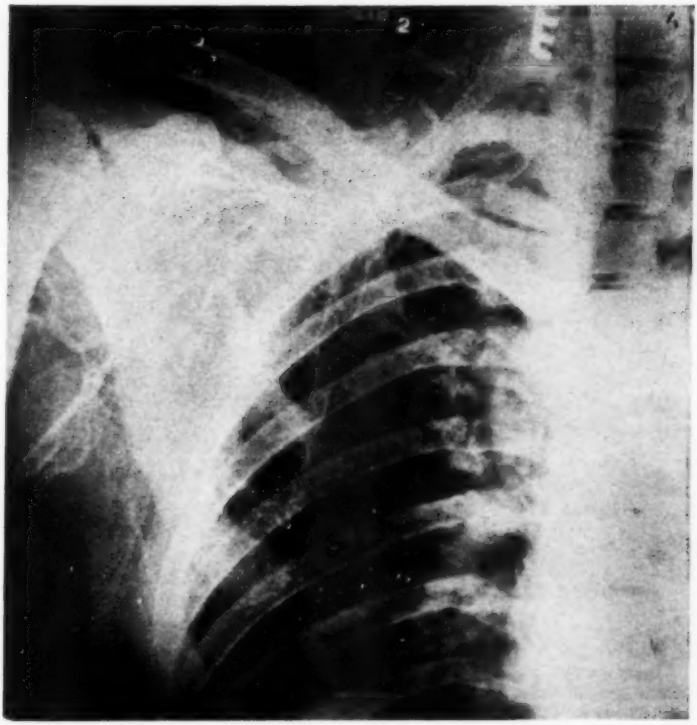


FIG. 2. B.

FIG. 2. Thrombosed subclavian aneurysm distal to cervical rib. Arteriogram obtained by injecting Thorotrast in a retrograde fashion into the right common carotid artery.

Case 4. This patient was a 12 year old boy who was admitted to the University of California Hospital on May 10, 1947, because of a large angioma involving the entire right arm, hand, and shoulder. The discoloration had been noted since birth and the patient had experienced recurrent attacks of pain, possibly associated with thrombophlebitis involving the venous component of the angioma. There was no osteohypertrophy but there was considerable soft tissue enlargement. Although there was no bruit audible over the right upper extremity the skin was warmer than on the normal side and it was felt that there might be some arterial component to the angioma. Accordingly, on May 9, 1947, a retrograde injection of the arteries of the right upper extremity was performed through the right radial artery. Under general anesthesia the right radial artery was occluded at the wrist and 30 c.c. of 35 per cent Diodrast were injected in retrograde fashion through a 16 gauge needle. Serial roentgen-ray films were taken. The needle was then removed and an attempt made to suture the artery but because of the trauma from the needle puncture thrombosis took place. However, there was no impairment of circulation to the hand. The films (figure 3) showed a normal arterial supply to the right upper extremity but

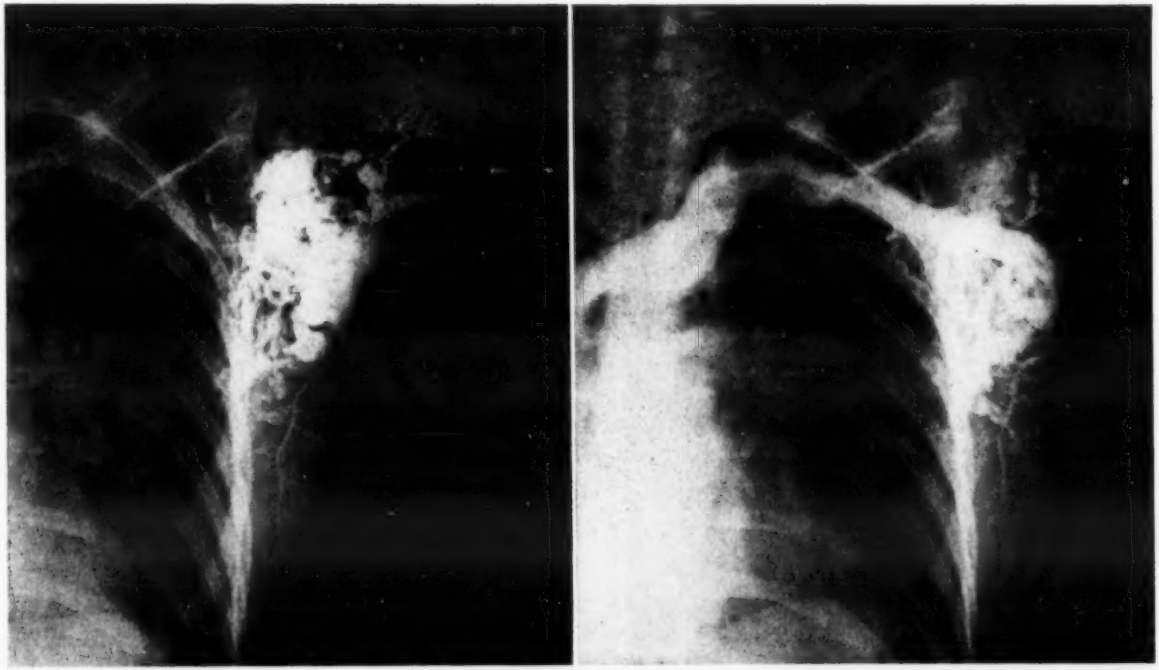
tremendous enlargement of the superficial veins. On May 22, 1947, the venous angioma of the palm of the right hand and little finger was resected. Necrosis of the distal half of the little finger followed this operation but removal of this portion of the angioma resulted in a great decrease in the size of the veins on the dorsum of the hand and forearm.

FIG. 3. Angiograms of the right upper extremity obtained by injecting 35 per cent Diodrast into the radial artery. The first film shows the filling of the arterial tree. The second film shows the filling of the greatly dilated veins.

Comment: Retrograde arteriography in this patient was useful in showing that there was no significant arterial component to the angioma. Although possible, injection of the main artery proximal to the lesion would have been difficult.

Case 11. This patient was a 34 year old female who was admitted to the University of California Hospital on February 11, 1948, because of a large swelling over the left scapula which had been present for three years. Operation previously performed at another hospital had revealed an angioma but the bleeding had been so severe that only a small portion of the lesion was excised for histological examination.

On physical examination there was marked pulsation of the axillary artery with a continuous thrill and bruit over the vessels high in the axilla. The mass over the dorsum of the scapula was pulsatile but quite firm and rubbery. The circumflex scapular vessels and the long thoracic artery were dilated. Upon occlusion of the subclavian artery the pulse rate dropped from 88 to 76 beats per minute. There was no enlargement of the heart nor decreased exercise tolerance.



A B

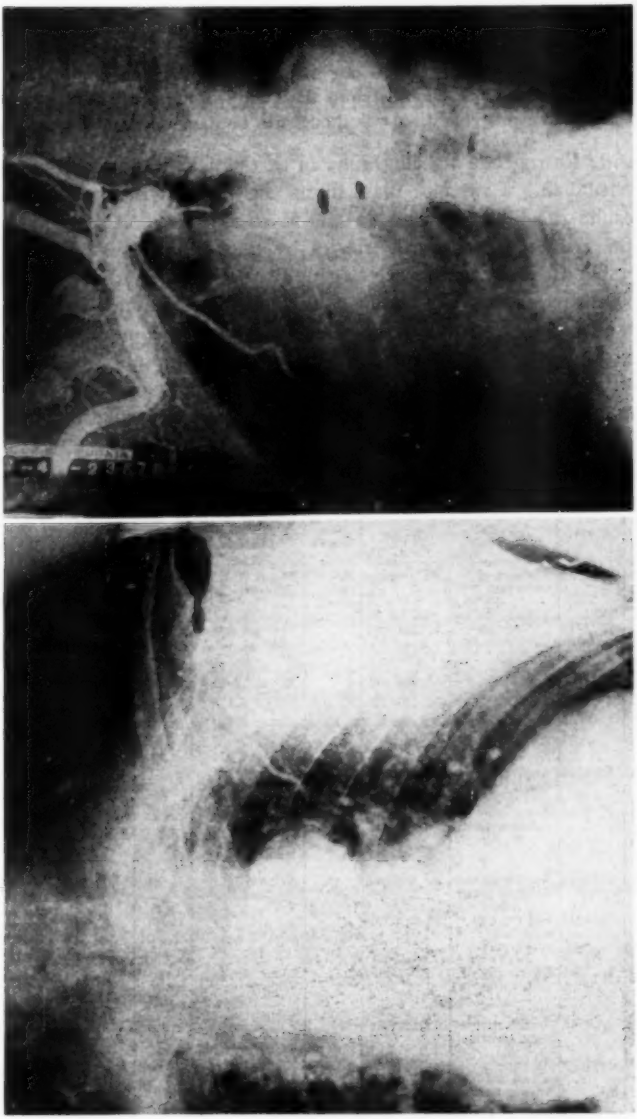
FIG. 4. Arteriogram of a congenital arteriovenous fistula of the left axillary and scapular vessels obtained by injecting 70 per cent Diodrast in a retrograde fashion into the brachial artery.

Retrograde arteriography was performed on February 14. The brachial artery was exposed below the profunda and by means of a 16 gauge needle 30 c.c. of 70 per cent Diodrast were rapidly injected. Serial roentgen-ray films were taken. As shown in figure 4 there was a large communication between the brachial artery and the angiomatous mass which filled the left axilla. The second film showed that the Diodrast passed into the venous side of the circulation so that an angiocardiogram was obtained. At operation on February 20, 1948, the left axillary artery was surrounded by a segment of rubber tubing and all the branches were divided and ligated from the clavicle down to the fistulous communication which was found to be just distal to the subscapular artery. This communication was closed with a transverse suture and the continuity of the artery restored. Following closure of the arterial component of the angioma the subscapularis and infraspinatus muscles were excised with the axillary contents. Except for temporary edema of the left arm the patient recovered completely from this operation, and there has been no recurrence of the bruit. Histological section revealed an angioma which was invading the muscles but which was composed of mature cells.

Comment: Retrograde arteriography in this patient was useful in visualizing an arteriovenous fistula located high in the left axilla. The brachial artery was severely traumatized by insertion of the 16 gauge needle so that several stitches of No. 00000 Deknatel were necessary to control bleeding following release of the artery clamps. It is believed that thrombosis probably took place at the suture line since the pulse on the left side was diminished in volume immediately following the arteriogram. However, there was no impairment of the circulation to the left hand. In retrospect, it would have been quite as satisfactory to have performed the arteriogram by direct injection of the contrast medium into either the subclavian or the axillary arteries.

Visualization of aneurysms of the thoracic aorta and innominate artery was attempted on three occasions but the results were not entirely satisfactory, presumably because of the difficulty of introducing a sufficient quantity of radio-opaque material rapidly. In one patient a complication resulted.

Case 6. This patient had been admitted to the University of California Hospital on numerous occasions since August, 1945, because of swelling of the left arm and neck with a bruit audible in the left ear. He was 70 years old at the time he was first admitted and had noted rather rapid onset of swelling of the left arm, forearm, and hand five weeks before entry. Angiocardiograms with intravenous injection of 50 c.c. of 70 per cent Diodrast through a 16 gauge needle into the left antecubital vein showed simply venous obstruction in the mediastinum with filling of collateral veins. On September 3, 1945, 20 c.c. of 70 per cent Diodrast were injected both into a vein of the right arm and into a vein of the left arm and these injections revealed a mediastinal mass which brought about a high degree of obstruction of the subclavian vein on the left although the right side was not completely blocked. Filling of the mass was not observed. Retrograde brachial arteriogram on June 3, 1947, with 50 c.c. of 35 per cent Diodrast failed to outline the aorta. However, when 50 c.c. of 70 per cent Diodrast were injected in the same fashion the aorta was outlined. An aneurysm involving the descending portion together with a large mass filling the anterior



A B

FIG. 5. Aneurysm of aortic arch. *A*. Phlebogram of left arm showing obstruction of the innominate vein. *B*. Arteriogram obtained by injecting 70 per cent Diodrast in a retrograde fashion into the right brachial artery.

superior mediastinum was made out (figure 5). The tortuous innominate artery could be seen.

Immediately after the injection of the contrast medium the patient had a convulsion, and for a period of several hours was in a state of markedly depressed circulation. This complication probably is attributable to the fact that no attempt was made to block the passage of Diodrast into the right carotid artery. Spontaneous recovery took place but his condition was thought to be inoperable.

Comment: Retrograde arteriography in this patient was moderately successful in visualizing a vascular mass filling the superior mediastinum.

The results in all the patients in whom an attempt has been made to visualize the aorta or peripheral arteries by retrograde arteriography are shown in table 1. Retrograde arteriography was done by direct puncture of the exposed artery, with injection of the contrast medium through a 15 or 16 gauge needle. Thrombosis of the artery occurred in three patients, although distal ischemia was not produced. Convulsions occurred in two patients with the use of 70 per cent Diodrast. In both of these cases the Diodrast was not prevented from entering the cerebral circulation.

TABLE I

Case No.	Sex	Age	Date	Clinical Diagnosis	Artery	Size Needle	Contrast Medium	Anesthetic	Complications	Comments
1	M	60	10/15/46	Abdominal aneurysm	Rt. femoral	No. 9 catheter	20 c.c. 70% Diodrast	Local	Thrombosed femoral	Normal aorta confirmed at operation
2	M	41	1/27/47	Subclavian aneurysm	Rt. carotid		20 c.c. Thorotrast	Local	0	Thrombosed aneurysm confirmed at op.
3	M	46	2/28/47	Left iliac thrombosis	Lt. femoral		20 c.c. Thorotrast	Local	0	Unsuccessful
4	M	12	5/ 9/47	Angioma right arm	Rt. radial	16	30 c.c. 35% Diodrast	Ether	Thrombosed artery	Venous angioma
5	F	55	5/18/47	Aneurysm abdominal aorta	Lt. femoral	16	40 c.c. 35% Diodrast	Gas Oxygen	0	Unsuccessful
6	M	72	6/ 2/47	Aneurysm thoracic aorta	Rt. brachial	16	50 c.c. 35% Diodrast 50 c.c. 70% Diodrast	Local	Convulsion	Aneurysm arch aorta
7	F	30	6/25/47	Aneurysm abdominal aorta	Rt. femoral	15	30 c.c. 70% Diodrast	Local	0	Unsuccessful
8	M		12/13/47	Retroesophageal right subclavian	Rt. brachial			Local	0	? Aneurysm thoracic aorta
9	F	52	1/ 7/48	Obliterated abdominal aorta	Rt. femoral	16	20 c.c. 20% Thorotrast	Avertin—local	0	Unsuccessful
10	F		2/ 3/48	Aneurysm right carotid	Rt. brachial			Local	0	Unsuccessful
11	F	34	2/14/48	Arteriovenous fistula with angioma axilla.	Lt. brachial	16	30 c.c. 70% Diodrast	Local	Thrombosed artery	Fistula and angioma confirmed at operation.

Discussion

Although arteriography can best be accomplished by the injection of radio-opaque material into the artery proximal to the lesion to be studied, occasionally the location of the lesion or its character makes it difficult to carry out this technic. Under such circumstances, retrograde arteriography may offer a method for adequate visualization. We have not been successful in our attempts at visualization of the abdominal aorta except in the patient in whom the catheter was introduced through a cannula inserted into the femoral artery (figure 1). In animal experiments Farinas showed fluoroscopically that to be successful the injection must first overcome the inertia of the blood flow and, second, must overcome the blood pressure. It may be that injection of a larger quantity of solution under higher pressure would have yielded more satisfactory results. The danger of thrombosis at the site of injection, especially where a large needle is inserted into a small artery, is very real. This thrombosis occurred in three of the patients shown in table 1. With the use of 70 per cent Diodrast, the possibility of serious systemic reaction should be considered, especially when there is any opportunity for the contrast medium to enter the cerebral circulation. Although iodine compounds are known to induce spasm,[12] we have not hesitated to use this material in the peripheral arterial lesions, provided there was no impairment of circulation.

Conclusions

1. Retrograde arteriography has been used in 11 patients for visualization of vascular lesions involving the peripheral arteries, and the abdominal and thoracic aorta.

2. Retrograde arteriography can be used in those patients in whom it is difficult or impossible to introduce the radio-opaque substance into the artery proximal to the lesion.

3. Attention is called to the complications which may result from the use of this method.

BIBLIOGRAPHY

1. Sicard, J. A., and Forestier, G.: Injections intravasculaires d'huile iodée sous controle radiologique, Compt. rend. Soc. de biol., 1923, lxxxviii, 1200.
2. Berberich, J., and Hirsch, S.: Die röntgenographische Darstellung der Arterien und Venen am lebenden Menschen, Klin. Wchnschr., 1923, ii, 2226.
3. Brooks, Barney: Intra-arterial injection of sodium iodid, preliminary report, Jr. Am. Med. Assoc., 1924, lxxxii, 1016.
4. Dos Santos, R., Lamas and Caldas: Artériographie des membres et de l'aorte abdominale, 1931, Masson et Cie, Paris.
5. Nelson, O. A.: Arteriography of abdominal organs by aortic injection, a preliminary report, Surg., Gynec. and Obst., 1942, lxxiv, 655.
6. Doss, A. K.: Translumbar aortography—an apparatus for injecting the radiopaque media, Surgery, 1944, xvi, 422.

7. WAGNER, F. B., JR.: Arteriography in renal diagnosis: preliminary report and critical evaluation, Jr. Urol., 1946, lvi, 625.
8. BLAKEMORE, A. H.: Angiography—an evaluation of its usefulness, Surg. Clin. N. Am., 1946, xxvi, 326.
9. HOYOS, J. M., and DEL CAMPO, C. G.: Angiography of the thoracic aorta and coronary vessels, with direct injection of an opaque solution into the aorta, Radiology, 1948, l, 211.
10. FARINAS, P. L.: A new technique for the arteriographic examination of the abdominal aorta and its branches, Am. Jr. Roent., 1941, xlvi, 641.
11. WAGNER, F. B.: Complications following arteriography of peripheral vessels, Jr. Am. Med. Assoc., 1944, cxxv, 958.
12. FARINAS, P. L.: Retrograde abdominal aortography, Am. Jr. Roent., 1946, lv, 448.

THE TREATMENT OF ACUTE PUTRID LUNG ABSCESS WITH PENICILLIN AND SULFADIAZINE *

By BARNET P. STIVELMAN, M.D., F.A.C.P., and JULIUS KAVEE, B.S. M.D.,
New York, N. Y.

ACUTE putrid lung abscess is one of the most serious of intrathoracic diseases. On the one hand it may lead to an early fatal termination because of toxemia, hemoptysis, embolic phenomena, spill over to the contralateral lung and rupture into the pleura. On the other hand, if an early fatal issue does not ensue, the acute becomes a chronic lung abscess which rarely resolves and requires extensive and difficult surgical intervention and, at best, a prolonged and costly convalescence if recovery or improvement is to be hoped for.

Spontaneous recovery from acute putrid lung abscess occurs in but a small percentage of cases. At the Harlem Hospital in the past few years spontaneous recoveries were noted only in 11 per cent of 70 patients with this disease. The favorable outcome occurred in patients with small, uncomplicated abscesses, little toxemia and limited perifocal pneumonitis.

Numerous remedies have been suggested in the treatment of this disease. Indeed many chemicals, autogenous and stock vaccines, postural drainage, bacteriophages, and even pneumothorax have come in for therapeutic praise by various observers. But the fact that the reported successes have not been reproduced with the respective methods of care in any large group of such patients prompts the suggestion that the cures reported might have occurred spontaneously.

With the advance in our knowledge of the pathogenesis and pathologic physiology of putrid lung abscess and the recognition of the ineffectiveness of treatment by medical means, it was inevitable that surgical intervention should be resorted to in their management.

At first it was felt that large abscesses, or those accompanied by great toxicity and slow roentgenologic improvement, were best treated by early thoracotomy and pneumonostomy. This was also true of abscesses which progressed and ruptured into the pleura, or gave rise to persistent hemoptysis.

In recent years, however, there has been a growing tendency to have all acute lung abscesses, regardless of their size or the severity of their toxic manifestations, treated surgically as soon as the diagnosis is made. This view received encouragement from the reports of many chest surgeons, notably Neuhof and Touroff,[1] who in 1940 reported 73 recoveries in 86 patients operated on for the relief of this condition. Sweet, on the other

* Received for publication July 1, 1947.
From the Chest Service of the Harlem Hospital, New York City.

hand, in the same year reported only 43 per cent cured of 125 patients treated surgically at the Massachusetts General Hospital. Sweet [2] was of the opinion that the results of surgical treatment of lung abscess were on the whole disappointing. He stated that if there is a good chance of spontaneous recovery, operation should be avoided. A similar view was expressed by Cutler [3] in 1936.

There are, however, no reliable criteria by which we can determine just when an acute lung abscess has reached a point when spontaneous recovery is no longer to be expected. On the other hand, waiting too long for such a recovery often results in the acute becoming a chronic abscess. In the first instance, because the lesion resolves slowly, we may expose the patient to a needless and often dangerous major operation, while if we procrastinate the resulting chronic abscess will require extensive surgical interference, attended by high mortality and morbidity and at best a prolonged, stormy and costly convalescence.

A consideration of these facts makes it quite obvious that we are in need of a treatment which would (1) increase the rate of recovery within the shortest possible period of time without surgical interference; (2) decrease the number and severity of pre- and post-operative complications in those who will have to be treated surgically.

When penicillin became freely available, we decided to study its potentialities in the treatment of putrid lung abscess and administered it to six patients with acute, and seven with the chronic form of this disease in 1944 and 1945. Sulfadiazine was employed concurrently, despite the fact that when used by itself it had given no relief in a small series of cases so treated. But its synergistic action with the antibiotic was becoming recognized, and it was hoped that it might have a beneficial effect on the ever present perifocal pneumonitis. The excellent results obtained and reported elsewhere [4] encouraged us to continue this method of treatment in 15 additional cases of acute putrid lung abscess in the past 15 months, and the 21 cases form the basis of this presentation.

As soon as a diagnosis of putrid lung abscess was definitely established and confirmed by chest roentgenograms, the patient was given both penicillin and sulfadiazine. The sodium salt of penicillin was administered intramuscularly in doses of 40,000 units every three hours. The sulfadiazine was given in the usual manner, sufficient to establish and maintain adequate blood levels. Occasionally much larger doses of penicillin were deemed desirable, and in a few cases we changed the brand of the antibiotic to obtain the desired results. But in no instance did we change the route or frequency of its administration. Moreover, the treatment was continued until all clinical and roentgenologic evidence of pulmonary involvement had disappeared.

Case Reports

Case 7. A man, 41 years old, entered the Harlem Hospital on December 12, 1945. In the past six months he had coughed on and off and had lost 16 pounds in weight. On the day of admission he had noted pain in the left chest, his temperature was 104° F. and his sputum was fetid. The initial chest roentgenogram revealed a moderate sized cavity with extensive pneumonic involvement in the left upper lobe. There were also small infiltrations in the right upper lobe. He was immediately placed on sulfadiazine and 25,000 units of penicillin every three hours. The infiltrations and the cavity began to regress and his temperature became normal on December 16, 1945. By January 9, 1946 the chest film revealed only a slight thickening of the pleura over the left upper lobe. The chest film of February 9, 1946 revealed no gross abnormality, and he was discharged as cured on February 11, 1946.

Comment: Uneventful recovery from a putrid lung abscess and some contralateral pneumonia with sulfadiazine and penicillin therapy.

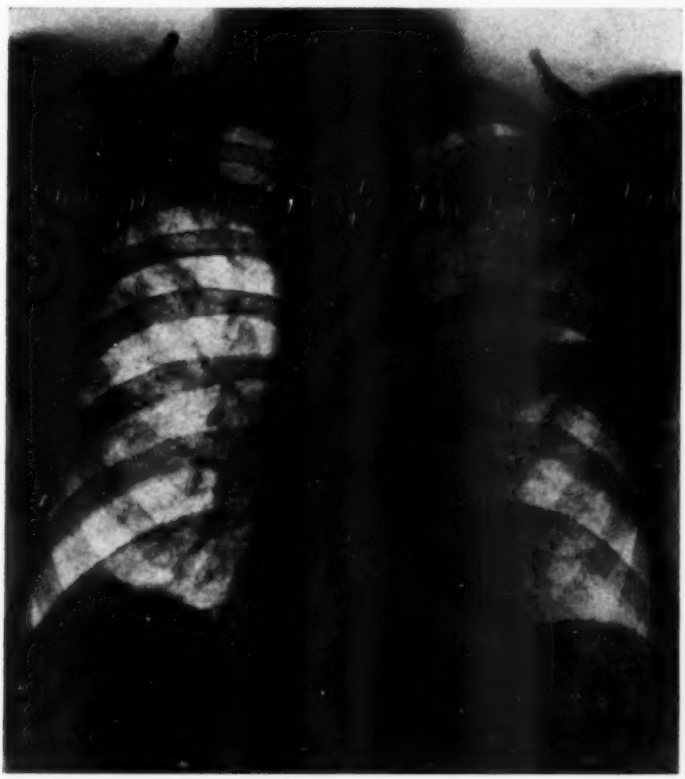


Fig. 1. *Case 7.* Film taken December 14, 1945 shows extensive cavitation with a wide fluid level in the left upper lobe.

FIG. 2. *Case 7.* Taken February 9, 1946. Shows both lungs clear.

Case 8. A man 26 years old, entered the pneumonia service of Harlem Hospital on December 30, 1945 complaining of shortness of breath and a sore throat which was accompanied by fever, cough and a pain in the chest. His temperature was 103° F. and he was extremely toxic and jaundiced. A type 3 pneumococcus was recovered from the sputum. The chest film of January 2 revealed consolidation of the entire right upper lobe with patchy consolidation of both bases. He was treated with sulfadiazine until January 12, 1946 without any benefit. On January 12 the sputum became profuse and foul and a large cavity was noted in the right axilla. He was given 50,000 units of penicillin every three hours and by January 16 the temperature was normal. The chest film of January 25, 1946 revealed no abnormality except for two small emphysematous blebs in the right upper lobe. On February 15 the chest film was normal and he was discharged cured on March 1, 1946.

Comment: The patient had an extremely toxic acute putrid lung abscess with putrid pneumonia in both lower lobes. The administration of sulfadiazine failed to produce any improvement. The addition of penicillin in adequate dosage was followed by rapid and complete recovery.

Case 9. A man 54 years of age, was admitted to Harlem Hospital on January 6, 1946. He was a chronic alcoholic and had a history of cirrhosis of the liver. Three weeks before admission he noted a productive cough with dark sputum. A week later he had severe pain in his right chest. His temperature on admission was 104° F. He coughed severely and had foul sputum. His liver was enlarged to three and one-half fingers below the right costal margin. The initial chest film revealed a large cavity with a fluid level occupying one-third of the right upper lobe. There was also a pneumonic involvement of the right lower lobe. The heart was enlarged in the region of the left ventricle. He was given sulfadiazine on January 7, 1946, but his temperature rose to 105° F. On January 10 he received in addition 30,000 units of penicillin every three hours and this was continued until March 18, 1946. The chest film of January 18, 1946 revealed fluid filling the entire cavity, indicating a block of the draining bronchus. Despite this, the temperature had become normal on January 16, 1946 and remained normal until his discharge. The chest roentgenogram of January 24, 1946 again revealed a large cavity. Serial roentgenograms thereafter showed progressive clearing of the lung and the final film taken March 15, 1946 revealed a few fibrotic nodules in the right upper lobe. He was entirely free of symptoms and was discharged completely cured on April 15, 1946.

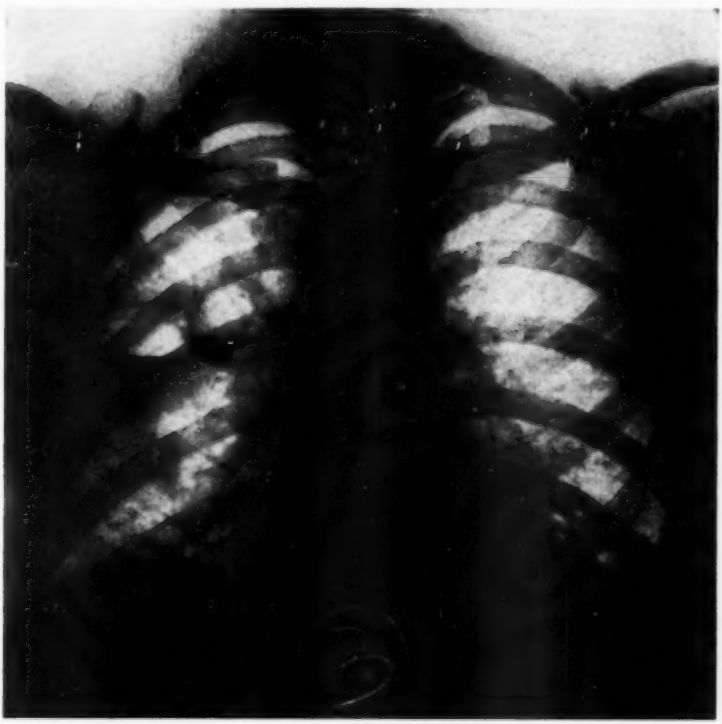


FIG. 3. *Case 8.* Film taken January 12, 1946 shows large abscess with fluid level in the right upper lobe.

FIG. 4. *Case 8.* Taken February 15, 1946. Shows clear lungs.

Comment: Complete recovery from a large acute putrid lung abscess with a blocked cavity under treatment with sulfadiazine and penicillin. This patient was in poor condition and had cirrhosis of the liver.

Case 10. A 32 year old Negro, a chronic alcoholic, entered the Harlem Hospital with foul sputum and a temperature of 102° F. on February 18, 1946. He stated that he had been sick for two weeks with a productive cough and fever. The chest roentgenogram revealed a large cavity with extensive pneumonic involvement in the upper lobe of the left lung. He was immediately placed on sulfadiazine and 25,000 units of penicillin every three hours. His temperature became normal on February 26, 1946, and continued normal until discharge. Serial chest roentgenograms showed progressive regression of the pneumonic area. The fluid level in the cavity disappeared on March 19, 1946, and the cavity was no longer visible a week later. When he was discharged on May 7, 1946, the chest film revealed a few fibrotic strands in the left upper lobe.

Comment: Uneventful recovery from a large acute putrid lung abscess with slight residual fibrotic change.

Case 11. A 32 year old Negro entered the Harlem Hospital on June 10, 1946, complaining of cough, weakness, expectoration of greenish sputum following exposure to wet weather a week before. On admission his temperature was 102° F. His sputum was foul and copious. There were moist râles and dullness throughout the right lower lobe. The initial chest film revealed a large abscess with fluid level surrounded by large nodular pneumonic infiltration scattered throughout the entire right lower lobe. He was given sulfadiazine and 30,000 units of penicillin every three hours. Despite this, the temperature rose to 104° F. By June 17, the serial chest films revealed a marked spread of the disease to the left lung. The penicillin was raised to 50,000 units every three hours. Nevertheless he became extremely cyanotic and dyspneic and there was a further spread throughout both lungs. He was extremely toxic and gravely ill, and the surgical consultant felt he would not survive operative interference. He was given oxygen, intravenous feedings and transfusions

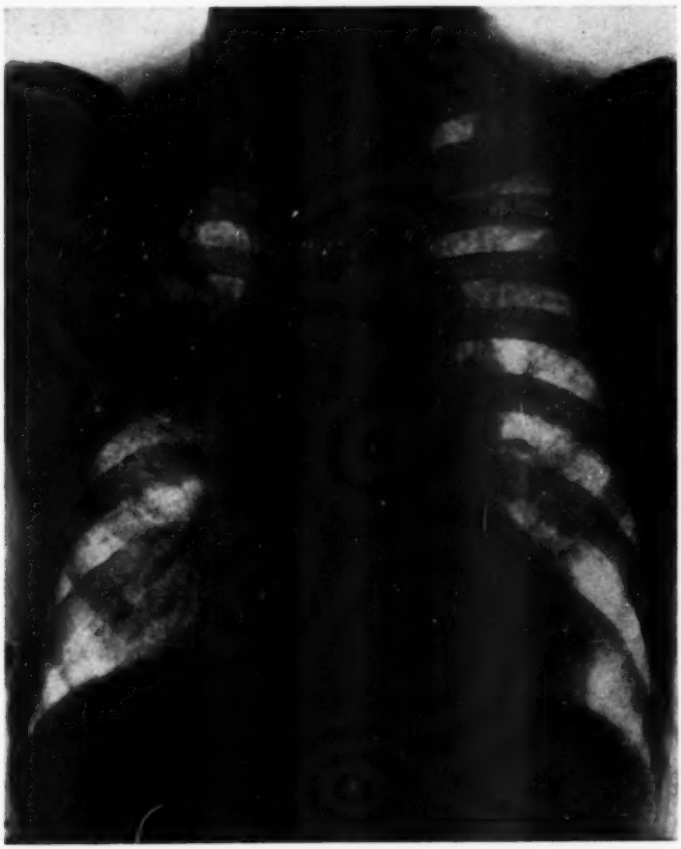


FIG. 5. *Case 9.* Taken January 8, 1946. Shows very large abscess occupying major portion of right upper lobe.

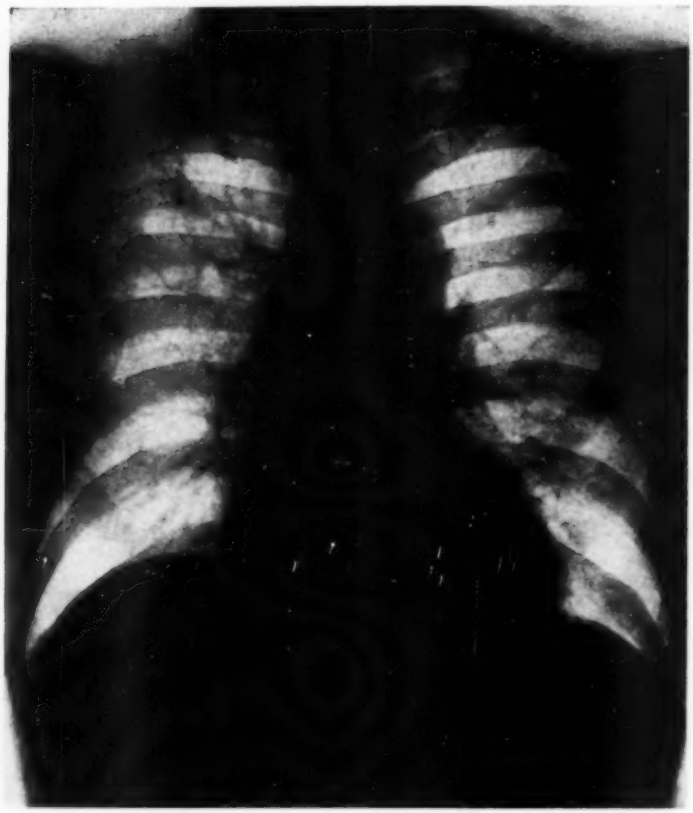


FIG. 6. *Case 9.* Taken March 26, 1946. Shows no evidence of abscess.

and the penicillin was raised to 100,000 units every three hours on June 27, 1946. The following day the temperature began to fall and the chest film of July 1 showed some slight improvement. By July 15 the temperature had returned to normal. He was no longer toxic and the infiltrations in the left lung had disappeared. On August 6, 1946 the cavity in the right lung was no longer visible. On August 13 the chest film failed to reveal any abnormality except for slight fibrosis in the medial aspect of the right lower lobe. The penicillin was discontinued on August 15, and he was discharged cured on September 4, 1946.

Comment: The patient was extremely toxic and sustained an early spill-over to all lobes on both sides. It was thought that he would not survive surgical care. We were not able to study the resistance of the infecting organisms to the penicillin used, but there can be no doubt that the patient's

life was saved by the increase in the dose of the antibiotic and persistence of its administration.

Case 12. An epileptic, *27* years of age, entered the Harlem Hospital on June 16, 1946. She had been ill for 10 days with chills, fever and a productive cough. Her temperature was 104° F. on admission, and the initial chest film on June 20 revealed a cavity in the right upper lobe. Foul sputum was noted on June 22. She had been given sulfadiazine and 25,000 units of penicillin intramuscularly every three hours since her admission without benefit. The penicillin dosage was therefore raised to 40,000 units on June 21. No improvement was noted by June 25 and surgery was contemplated. However, on June *27* the temperature became normal. By July 8 the lung had cleared markedly and the film of July 15 no longer revealed cavitation.

FIG. 7. *Case 11.* Film taken June 11, 1946 shows large abscess in the right upper lobe.

FIG. 8. *Case 11.* Taken July 7, 1946. Shows marked spillover to the opposite side.

On July 23, while the right side was clearing, a small pneumonic infiltration was noted in the left lower lobe, and the penicillin was raised to 50,000 units per dose. Improvement ensued and the chest film of July 27 revealed no abnormality. Bronchography on August 7 was normal. Penicillin was discontinued on August 25, 1946. She was discharged as cured of her lung abscess on September 14, 1946.

Comment: This case again illustrates the need of increasing the dosage of penicillin when clearing of the lesion is retarded, or when a spillover ensues.

Case 13. A 36 year old man was admitted to Harlem Hospital on August 14, 1946 with a history of seven days' illness, cough, expectoration and fever. His temperature was 103° F., and he had copious foul expectoration. The initial chest film showed consolidation of the entire right upper lobe with a high-light suggesting early cavitation. Sulfadiazine was started on the day of admission, but there was no effect

upon the temperature. On August 18 he was given in addition 50,000 units of penicillin intramuscularly every three hours. The temperature fell by lysis and was normal after August 22, 1946. However, the chest film of August 27, 1946 revealed a large cavity, although there was much less pneumonitis. Penicillin was continued and the chest roentgenogram of September 11 no longer revealed cavitation. The final roentgenogram of October 1, 1946 showed no abnormal shadows. He was discharged cured on October 3, 1946.

Comment: Complete and rapid recovery from a large putrid lung abscess under treatment with sulfadiazine and penicillin.

Case 14. A 36 year old man entered the Harlem Hospital on September 8, 1946 with a temperature of 104° F. For two weeks he had had chills, fever, weakness and a productive cough. On September 7 his sputum became foul. Initial chest roentgenogram revealed a consolidation of the right upper lobe, and he was given sulfadiazine and 40,000 units of penicillin every three hours. This dose was continued

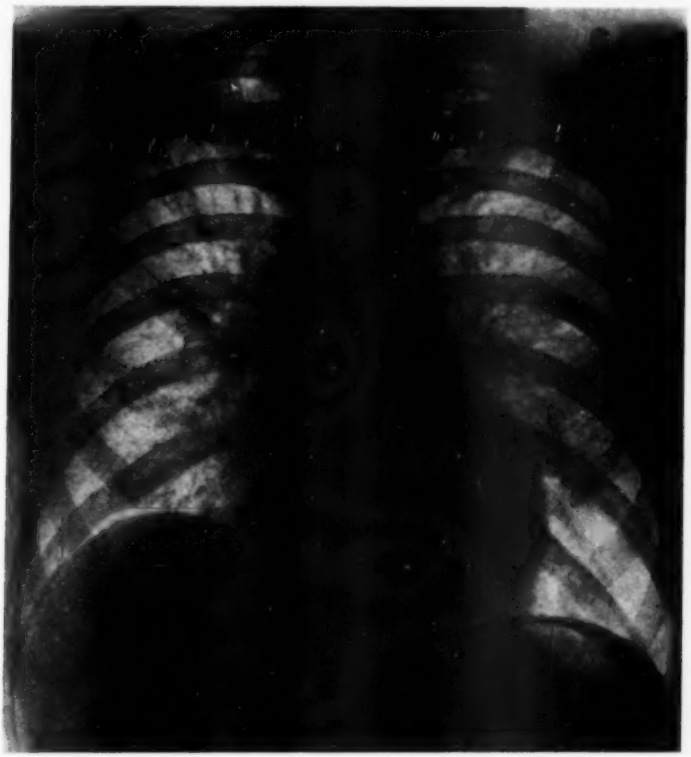


FIG. 9. *Case 11.* Taken August 20, 1946. Shows clear lungs.

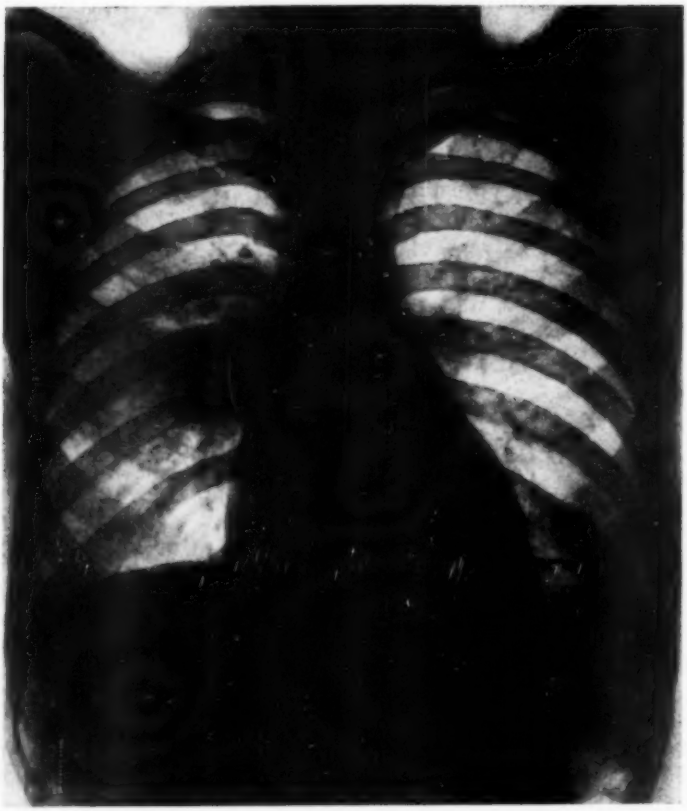


FIG. 10. *Case 12.* Taken September 22, 1946. Shows large cavity in the right upper lobe with fluid level.

until his discharge. On September 14, although there was no change in the chest film of that date, the temperature had become normal and the foul odor of his sputum disappeared. The chest film of September 21, 1946 revealed marked clearing with residual pleural thickening and an elevated right diaphragm. The final roentgenogram of October 1, 1946 revealed slight thickening of the pleura. He was discharged on October 3, 1946.

Comment: Acute putrid lung abscess which was cured promptly with sulfadiazine and penicillin.

Case 15. A 26 year old Negress entered the Harlem Hospital on September 21, 1946 complaining of increasing pain in the right chest of two weeks' duration. She had chills, fever, and bloody sputum, and her temperature on admission was 104° F. The initial chest film revealed a 3 cm. cavity within a pneumonic infiltration in the

upper portion of the right lower lobe. The sputum was copious and foul. She was started immediately on sulfadiazine and penicillin (50,000 units every three hours). Her temperature reached the normal on September 26 and the penicillin dosage was reduced to 30,000 units. On October 4 the cavity had disappeared and the penicillin dose was further reduced to 20,000 units. On October 21, 1946 the chest film was clear, and she was discharged as cured on October 25, 1946.

Comment: Uneventful recovery from an acute lung abscess with penicillin and sulfadiazine therapy.

Case 16. A 24 year old Negress entered the Harlem Hospital on December 9, 1946. She had had chronic upper respiratory disease for one year. Three weeks prior to admission her cough became much worse and the sputum became blood tinged. Two weeks later she noted foul sputum and fever, and experienced inspiratory pain in the right chest. On admission her temperature was 101° F. Dullness and numerous moist râles were elicited over the right lower lobe posteriorly. The ad-

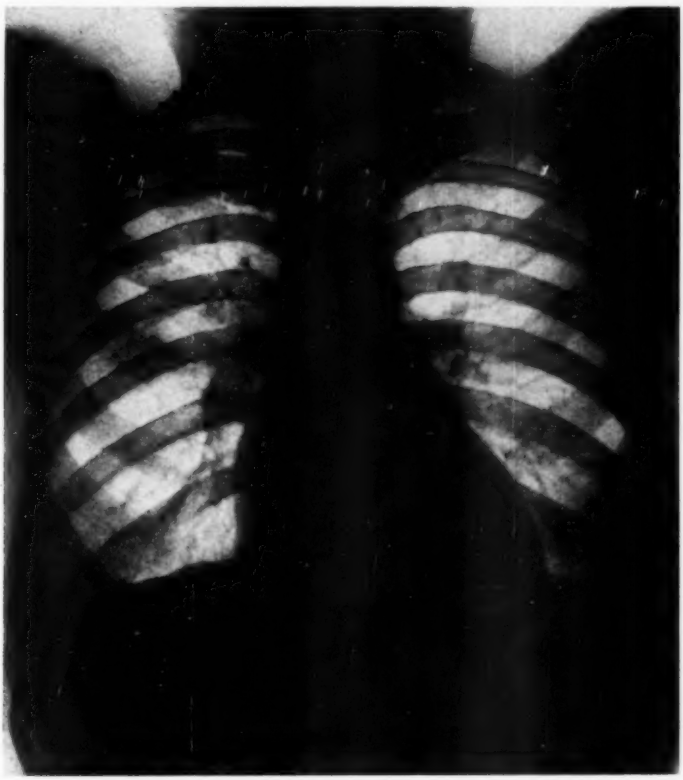


FIG. 11. *Case 12.* Taken October 21, 1946. Shows no evidence of abscess.

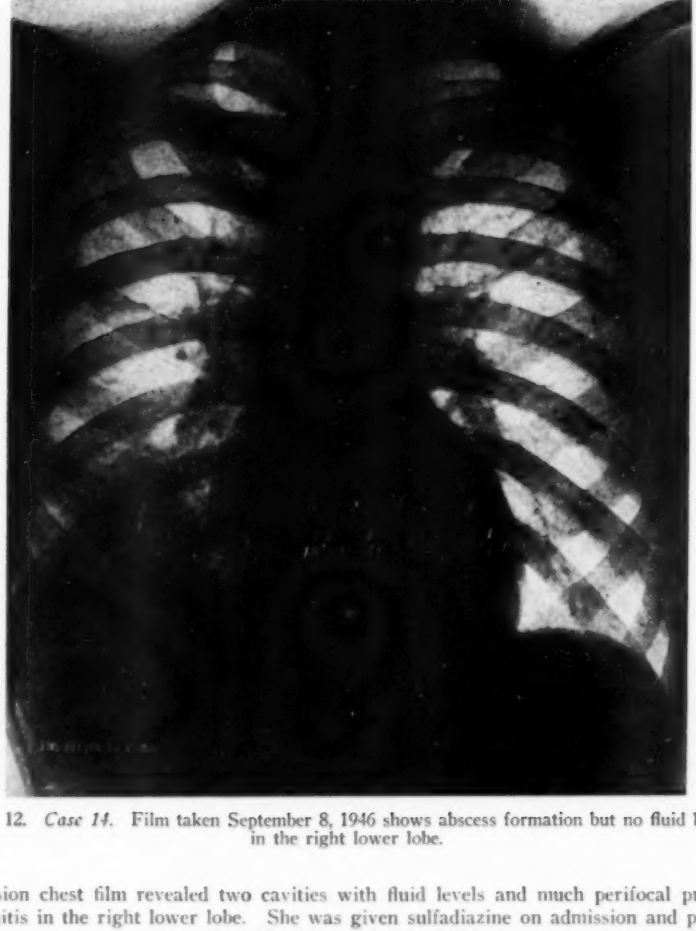


FIG. 12. *Case 14.* Film taken September 8, 1946 shows abscess formation but no fluid level in the right lower lobe.

mission chest film revealed two cavities with fluid levels and much perifocal pneumonitis in the right lower lobe. She was given sulfadiazine on admission and penicillin was started on December 13, 1946, in doses of 50,000 units every three hours. This therapy was continued until her discharge. The sputum ceased to be foul and the temperature became normal on December 15, 1946. The chest film of December 26, 1946 failed to reveal any cavities and by January 15 the roentgenogram was that of a normal lung. Lipiodol bronchography on January 20, 1947 failed to reveal any abnormality of the lower lobes of the lung. She was discharged as cured on January 31, 1947.

Comment: Uneventful cure of multiple lung abscesses with penicillin and sulfadiazine.

Case 17. An asthmatic 24 year old Negress was admitted to the Surgical Ward of the Harlem Hospital on November 18, 1946, where a subtotal thyroidectomy was done for a non-toxic thyroid adenoma. She was discharged feeling perfectly well, but on December 6, 1946 she began to cough and experienced pain in the right chest. Her cough soon became productive of large amounts of foul sputum. A few days later she noted marked pain in the right shoulder extending down the arm. She was re-admitted to Harlem Hospital on December 15, 1946 with a temperature of 102.8° F.

There were scattered sibilant râles throughout both lungs, as well as numerous large moist râles in the right base and axilla. There was marked tenderness over the right chest in the region of the sixth and seventh dorsal nerves and over the right shoulder joint. She was given sulfadiazine for four days without any effect on the temperature. On December 19 she was given 30,000 units of penicillin every three hours in addition to the sulfadiazine. The initial roentgenogram revealed an area of consolidation of about 4 cm. in diameter in the region of the right costophrenic sinus. (Careful reëxamination of this film on January 22, 1947 showed the presence

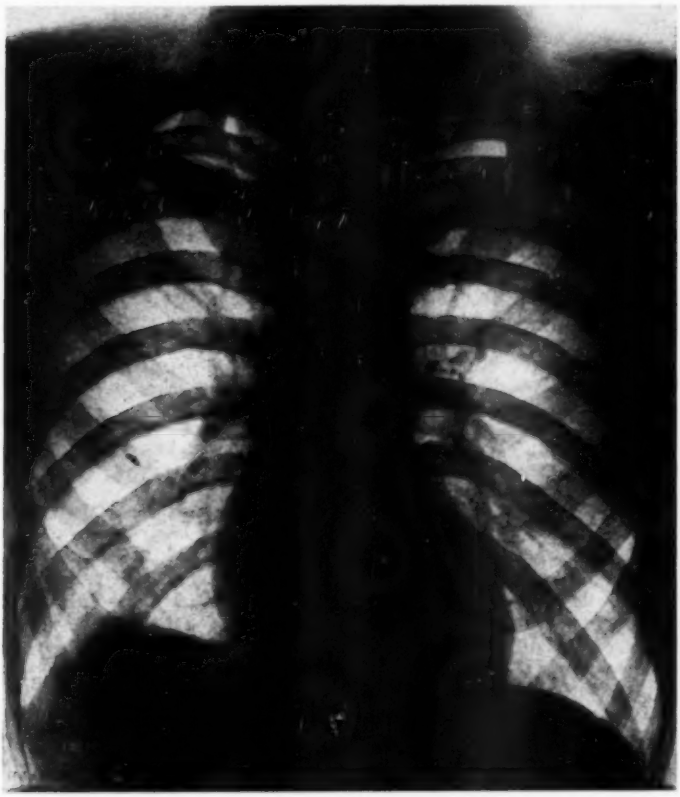


FIG. 13. *Case 14.* Taken October 1, 1946. Shows a clearing of the lesion.

of a cavity in the area first thought to be an infarct or pneumonia.) Two days after the penicillin was started the temperature became normal and the cough and expectoration diminished greatly. The penicillin and sulfadiazine were discontinued on January 5, 1947 because of a provisional diagnosis of pulmonary infarct. A paravertebral block of the fifth, sixth and seventh dorsal nerve routes was done on January 17, 1947, with temporary relief of the severe pain in the chest and shoulder. The chest films of January 15 and 20 revealed a gradual increase of the area of consolidation with cavity formation. Sulfadiazine and 100,000 units of penicillin every three hours were again administered and continued until she left the hospital. The chest films of February 24, 1947 and March 10, 1947 showed complete disappearance of the cavity and the area of consolidation almost completely resolved. She left against advice on March 12, 1947.

Comment: A case of abscess in the lung following thyroidectomy, in whom the penicillin injections were for a time discontinued because of symptomatic improvement and a temporary diagnosis of pulmonary infarction. Restudy of the early films showed cavitation. The lesion cleared when patient was again placed on sulfadiazine and penicillin in large doses.

Case 18. A 36 year old Negress entered the Harlem Hospital on January 5, 1947. She had had a cough for one month, and pain in the left chest and fever for two weeks prior to admission. She expectorated foul and bloody sputum. She felt nauseated, vomited frequently and had nightly sweats.

She had a temperature of 104° F. and was acutely ill. The breath and sputum were extremely foul. Numerous moist râles were heard over the right base posteriorly and at the right axilla. The initial chest film revealed an area of consolidation, as well as a cavity with a fluid level in the right lower lobe. The sputum contained no acid-fast bacilli, and on culture a *Streptococcus hemolyticus* alpha and *Staphylococcus albus* were noted. Sulfadiazine was administered for three days without effect. On January 8 penicillin in 40,000 unit doses every three hours was added, and continued until her discharge. Her temperature became normal on January 10. By January 25, 1947 the cavity could no longer be visualized, and there was a marked decrease in the pneumonic reaction. On February 4 there was further clearing of the pneumonic infiltration. She has had no symptoms or sputum since January 10, 1947. She left against advice on February 10, 1947.

Comment: Lung abscess cleared when penicillin was added to the treatment with sulfadiazine.

Case 19. A 29 year old Negro entered the Harlem Hospital on February 8, 1947. He had had fever for two weeks, and 10 days before admission had noticed bloody and foul sputum. He complained of a severe pain in his left chest and a loss of 12 pounds in weight.

On admission his temperature was 100° F. and he had profuse and foul expectoration. The initial chest film revealed a rounded infiltration in the mid-zone of the left lung, with a 3 cm. cavity at its center. He was immediately given sulfadiazine and 40,000 units of penicillin every three hours. The sputum was negative for acid-fast bacilli. In three days the cough, expectoration and pain had disappeared. A chest film taken 10 days after admission showed marked clearing of the pneumonic consolidation. On February 24 the chest film showed further clearing. On March 4 a generalized erythematous rash was noticed, and since this was believed to be due to sulfadiazine, its administration was discontinued. The chest film of March 11, 1947 revealed normal lung fields. Penicillin was continued until discharge on March 18, 1947.

Comment: Cure of acute putrid lung abscess with penicillin and sulfadiazine.

Case 20. A chronic alcoholic 21 year old Negress entered the Harlem Hospital on February 10, 1947, complaining of cough, fever and pain in the chest of six days' duration. Her sputum was profuse and foul. In April 1946 she had had a chancre which was treated at another hospital with penicillin.

On admission her temperature was 103° F. and she appeared gravely ill. Dullness and large moist râles were elicited over the right upper lobe anteriorly. The admission chest film revealed a 5 cm. cavity with a fluid level surrounded by an area of pneumonic infiltration. She was given sulfadiazine alone for three days without any effect. Thereafter she was given in addition 100,000 units of penicillin every three hours. On February 19, the temperature dropped by crisis and the sputum and cough disappeared. A chest film of February 21 showed the abscess to be half its original size and the pneumonic reaction had disappeared. On February 28 no cavity or pneumonic reaction could be noted. On February 25 a single sputum was positive for acid-fast bacilli; but because three sputa have been negative since and the lungs show no evidence of disease, we feel the positive report was due to clerical error. Bronchography was attempted on March 7, 1947, but she failed to coöperate.

Comment: Complete disappearance of large pulmonary abscess with penicillin and sulfadiazine.

As shown in table 1, 19 of 21 cases treated recovered and showed complete roentgenologic resolution of the lesion. One patient left against advice

TABLE I

Table Showing Results of Treatment in 21 Patients with Acute Putrid Lung Abscess with Penicillin and Sulfadiazine

No.	Patient	Sex	Age	Admission	Lesion	Temperature Returned to Normal and Clinical Symptoms Abated in	X-Ray Resolution in
1	T. J.	M	49	10/21/44	L.L.	5 days	37 days
2	I. R.	F	35	4/23/45	L.L., R.L.	10 days	59 days
3	L. M.	M	38	5/ 5/45	R.L.	7 days	65 days
4	A. P.	M	21	7/19/45	R.L., Interlob.	2 days	Interlobar Exudate
5	W. B.	F	28	7/20/45	R.L.	3 days	31 days
6	H. H.	F	37	11/10/45	R.L.	5 days	19 days
7	S. M.	M	41	12/12/45	L.U.	4 days	59 days
8	J. S.	M	26	12/30/45	R.U.	4 days	47 days
9	H. L.	M	54	1/ 6/46	R.U.	4 days	68 days
10	B. S.	M	32	2/18/46	L.U.	8 days	78 days
11	T. F.	M	32	6/10/46	R.U.	35 days	64 days
12	T. G.	F	27	6/16/46	R.U.	11 days	41 days
13	W. M.	M	36	8/14/46	R.U.	4 days	43 days
14	H. R.	M	36	9/ 8/46	R.L.	6 days	23 days
15	J. D.	F	26	9/21/46	R.L.	5 days	30 days
16	A. T.	F	24	12/ 9/46	R.L.	6 days	37 days
17	E. M.	F	24	12/15/46	R.L.	2 days	40 days
18	A. B.	F	36	1/ 5/47	R.L.	2 days	30 days
19	L. B.	M	29	2/ 8/47	L.U.	3 days	31 days
20	R. L.	F	21	2/10/47	R.U.	6 days	18 days
21	E. V.	M	56	1/ 6/47	R.U.	8 days	29 days Died of Brain Abscess 2/15/47

with an interlobar exudate between the right middle and lower lobes. Another patient, who will be reported in detail elsewhere, died with meningitis; and an autopsy revealed purulent meningitis as well as a fetid abscess in the left frontal lobe of the brain, but no evidence of putrid lung abscess.

The distressing symptoms abated, and the temperature returned to normal in two to 35 days after the beginning of the treatment. The average for the group was six days. Roentgenographic clearance of the lesion was noted in 18 to 78 days, with an average for the group of 42 days. The right lower lobe was the seat of the abscess in nine cases, and the left lower in one case. The right upper lobe was affected in seven cases, and the left upper in three. One patient had abscess formation in both the right and left lower lobes.

There were two recurrences among the 21 patients whose acute putrid abscesses had cleared under treatment. In one (case 12), an epileptic young woman, the new abscess recurred within five months in the lobe originally involved. She did well again with penicillin and sulfadiazine. The new abscess has almost completely disappeared, but there is still a linear band of radio-opacity at the base of the upper lobe and she is still under observation. In the second patient (case 10), a chronic alcoholic, the abscess recurred nine months after it had cleared. He claimed to have been ill over two months before his second admission. Penicillin failed to clear this chronic abscess, and the patient refused surgical treatment.

There was also a 36 year old Negro with putrid abscess in the right upper lobe. He did well with penicillin but refused further intramuscular injections before the lesion cleared. His abscess became chronic, but he was treated successfully with pneumonostomy and left the hospital five months after admission.

A 49 year old Negress, who claimed that she was ill for only three weeks with fever, cough and foul sputum, was found to have a markedly shrunken and fibrotic left lung with two oblong cavities in the upper lobe. It was felt that she had chronic abscess formation. Prolonged treatment with penicillin resulted in some clearing of the perifocal infiltration, but the cavities persisted and she refused surgical intervention.

Discussion

The increase in our knowledge of the pathogenesis of acute putrid lung abscess in the past two decades has led to universal recognition that this disease is a primary clinical and pathological entity. Once considered a frequent complication of lobar pneumonia, it is now well established that this concept is not supported by critical investigation.

At the Harlem Hospital, where for the past 20 years we have treated more than 400 cases of pneumonia yearly, putrid abscess of the lung was one of its rarest complications. Indeed, in the few doubtful cases we observed

in our wards and elsewhere, the diagnosis of pneumonia instead of abscess was made because fetid cough and expectoration were overlooked or were slow in coming, and chest roentgenograms were not routinely used.

The monumental work of Coryllos and Birnbaum,[5] showing that bronchial and bronchiolar obstructions are respectively the true causes of lobar and lobular atelectasis, contributed greatly to our understanding of certain aspects of pulmonary pathology. As a result of their observations, we know that the circulation in any lung segment has a direct relationship to its ventilation and drainage; and any area deprived of its ventilation, as is inevitable when bronchial obstruction and atelectasis supervene, suffers a corresponding loss of circulatory efficiency.

Cohen[6] and others have shown that when noxious material containing pathogenic anaerobic bacteria is aspirated into a small bronchus, the segment of the lung drained and ventilated by this bronchus can become the seat of a putrid abscess. It is reasonable to assume that the growth of the anaerobe is greatly encouraged by the local anoxemia in the atelectatic area distal to the point of bronchial obstruction.

While the aspiration of foreign bodies may cause putrid lung abscess in all age groups and endobronchial tumors in those usually past middle age, most lung abscesses are primary clinical and pathological entities and can develop in apparently healthy individuals. Severe alcoholics, and particularly those unconscious or stuporous following epileptic seizures and anesthesia, obviously are more prone to suffer from this disease.

The size of the abscess in no way affects the method of its care. A large abscess with a wide fluid level is not necessarily the result of extensive necrosis of the lung tissue involved. It is more often due to local obstructive emphysema. The weakened interalveolar septa may be ruptured by the increase in the pressure of the inspired air that cannot be expelled because of the partial bronchiolar obstructions secondary to inflammatory edema. That the lung segment involved is distended by the air under pressure is suggested by the almost geometrically perfect semicircle which forms the upper limit of the abscess, a phenomenon that does not support the presence of extensive destruction of tissue throughout the involved area.

Moreover, the rapid disappearance of the supposed large necrotic cavity, often within a few days after treatment is started, cannot possibly be due to rapid healing and restitution of the local structure. It can be more logically explained by the recoil of the distended segment of the lung once the bronchial obstruction due to inflammatory edema has been reduced by the action of the antibiotic, and normal ventilation and drainage reëstablished.

Our experience has shown that it is of utmost importance, if satisfactory results are to be obtained in cases with acute putrid abscess, to continue the combined administration of penicillin intramuscularly and sulfadiazine orally, not only until all toxic and local symptoms have disappeared, but until the chest film shows no abnormal shadows in the segment of the lung involved.

Chronic Putrid Lung Abscess

It is different in the case of chronic lung abscess. Here the lung and bronchi have been converted by the reaction to the prolonged putrid infection into a maze of fibrosis, multiple hard-walled cavities, bronchiectasis, atelectasis, and chronic pneumonitis, so that restitution to the normal cannot be hoped for with medical care. Often nothing short of lobectomy or pneumonectomy will save the life of the patient. Nevertheless, the combined penicillin and sulfadiazine administration was of inestimable value in the cases who were treated at the Harlem Hospital. It lessened toxicity, prevented further septic and metastatic foci, often cleared the surrounding pneumonitis, and improved the general condition of the patients so that they were better able to withstand the extensive operative interference indicated to bring relief.

Summary

1. Spontaneous recovery was noted in only 11 per cent of our 70 patients with acute putrid lung abscess.

2. Complete symptomatic and radiographic recovery was attained in 19 of 21 such cases treated with penicillin and sulfadiazine.

3. One patient died of a brain abscess, although his lung had cleared.

4. There were two recurrences of the lung abscesses; one in a girl who had frequent epileptic seizures, and the other in a severely alcoholic young man.

5. Abscess cavities of small and large dimensions disappeared with this method of care. The size of the abscess is most often determined by the degree of coexisting obstructive emphysema, rather than extensive local necrosis.

6. The salient feature in this method of treatment is the continuation of the administration of penicillin and sulfadiazine, not only until all toxic and local symptoms have disappeared, but until the chest roentgenogram shows no abnormal shadows in the segment of the lung involved.

7. Although no recoveries were noted in cases with chronic putrid lung abscess with this method of care, eight of 10 such patients became less toxic by virtue of the partial or complete clearing of the coexisting pneumonitis, and were better able to withstand the extensive surgical interference usually indicated.

8. In view of our experience, the concept that patients with acute putrid lung abscess require early surgical intervention deserves drastic revision.

BIBLIOGRAPHY

1. Neuhof, H., and Touroff, A. S. W.: Acute putrid abscess of lung: surgical treatments and results in 86 consecutive cases, Jr. Thorac. Surg., 1940, ix, 439–449.

Neuhof, H., Touroff, A. S. W., and Aufses, A. H.: Surgical treatment by drainage of subacute and chronic putrid abscess of the lung. Ann. Surg., 1941, cxiii, 209–220.

2. Sweet, R. H.: Lung abscess: analysis of Massachusetts General Hospital cases from 1933 through 1937, Surg., Gynec. and Obst., 1940, lxx, 1011–1031.
3. Cutler, E. C., and Gross, R. E.: Non-tuberculous abscess of the lung, Jr. Thorac. Surg., 1936, vi, 125–155.
4. Stivelman, B. P., and Kavee, Julius: Penicillin in the treatment of putrid lung abscess, Ann. Int. Med., 1946, xxv, 66–77.
5. Coryllos, P. N., and Birnbaum, G. L.: Obstructive massive atelectasis of the lung, Arch. Surg., 1928, xvi, 50.
Coryllos, P. N., and Birnbaum, G. L.: The circulation in the compressed atelectatic and pneumonic lung, Arch. Surg., 1929, xix, 1346.
6. Cohen, J.: Bacteriology of abscess of the lung and methods for its study, Arch. Surg., 1932, xxiv, 171–188.

CLINICAL EVIDENCE OF SENSITIVITY TO GONADOTROPINS IN ALLERGIC WOMEN *

By E. W. Phillips, M.D., F.A.C.P., *Phoenix, Arizona*

The concept that women may become sensitized to the hormones secreted by their own endocrine glands has occurred to a number of observers widely separated in time, place and viewpoint. For example, Finch [1] in 1938, and later (1940), published his finding that the nausea and vomiting of early pregnancy are allergic in origin and that they can be relieved by desensitization with a hormone derived from corpus luteum. My earlier reports on sensitivity to gonadotropins,[2] and on the technic of testing and the results of treatment with a preparation of gonadotropins,[3] appeared in 1942 and 1943. Zondek and Bromberg,[4] writing from Jerusalem in 1945, reported their investigation of allergic sensitivity to the steroid sex hormones. They dissolved these crystallized steroids in purified olive oil. Their positive reactions to intradermal testing with the steroids so dissolved were not the familiar wheal and flare; they were delayed, appearing from three to 48 hours after injection.

This test with steroid hormones in oil is rather inconvenient, and it is not easy to interpret. Thus, Waldbott [6] remarks, "In contrast with the observations of Zondek,[5] skin reactions with extracts of estrogenic substances were inconclusive upon intracutaneous testing." In the same article he states that 47 out of 148 asthmatic females of menstrual age gave a history of having had an aggravation of their allergic symptoms before their periods. In his summary he lists "sensitivity . . . to endocrine products (premenstrual aggravation!)" as among the most important causes of intrinsic asthma. There are many reports of sensitization to insulin. It seems reasonable to accept sensitivity to hormones, for which Zondek proposes the term "endocrine allergy," as a clinical entity.

This communication records two years' further experience in the use of the water soluble gonadotropins along the lines described in my preliminary report. In the hope that it would be of service in cutting down the recurrent disability of many women employed in Arizona's war industries, that report was published locally. Hence, it seems proper to quote from it freely, the more so because the methods and findings then recorded are supported by later work.

My interest in this subject was engaged through accident. An allergic woman patient suffered from menorrhagia and metrorrhagia. Synapoidin was administered intramuscularly and severe shock resulted. The patient recovered, and it was found that an immediate strongly positive reaction to

* Received for publication December 2, 1947.

an intradermal test with a 1:5 dilution of Synapoidin occurred. This woman, whose allergies had been thoroughly studied, was not sensitive either clinically or by skin test to any meat protein or animal emanation. Passive transfer tests, using non-allergic male recipients, were strongly positive to diluted Synapoidin. Control tests on numerous allergic individuals showed that males, female children below the age of puberty, and the majority of women reacted negatively to this test. Because of the probability that other allergic women might be similarly sensitized, a report [2] of this case was published. Clinical desensitization of this patient was then attempted, using the test dilution intradermally in treatment. Normal menstruation was restored.

Thereafter the test with 1:5 Synapoidin was made routinely on all females between the ages of 12 and 60 who were tested or treated for allergic disease. They had sought relief from various allergic ailments, chiefly from asthma but none specifically from premenstrual headache or tension. The test was, as before, 0.02 c.c. of a 1:5 dilution of Synapoidin, intradermally. The diluent was 5 per cent glucose (Unger's formula), the same diluent used for other allergens. Only those reactions with typical wheal, flare and itching were recorded as positive. In the course of six months, 118 women reacted negatively to this test; 25 others reacted positively. These latter when questioned related various complaints connected with or preceding their monthly periods.

The complaint most often heard was of headache, usually of the migraine type, but not necessarily a classic hemicrania. Usually this was accompanied or preceded by other unpleasant phenomena, such as malaise, vaguely localized pains, digestive disturbances and vertigo. Emotional instability, depression, insomnia and temperamental change were frequently reported, sometimes by a member of the family. Two girls had premenstrual exacerbation of acne. These manifestations, varying in kind and degree, were present in some cases as long as a week before they were ended by the menstrual flow. Most of these women said that, of course, their asthma (or whatever allergy had brought them under treatment) was worse at that time. They seemed to regard this periodic exacerbation as natural and inevitable, a part of the penalty of their sex.

Since most of the women reacting positively to Synapoidin required treatment for other allergic ailments, it was convenient to administer the gonadotropin at the same time. The initial test dose was cautiously increased, and for the reason that a potent biologic agent was being used, the dose was kept consistently low. Synapoidin was always injected separately, so that the local reaction could be observed. In most cases it was vigorous.

The results of treatment in this preliminary group were favorable, especially in the relief of premenstrual headache and tension. The schoolgirls with premenstrual acne showed noticeable improvement. One girl with prepubertal exacerbation of a lifelong asthma was improved (later, normal

menstruation was established). The therapy was so helpful to the limited number of patients concerned that a preliminary report [3] was made.

Since that publication 81 additional patients reacting positively to the intradermal test have been observed and treated. Many of these women were referred, but none by gynecologists. Consequently such conditions as pruritus vulvae have not been encountered. The cases of this second series differ somewhat from those of the first. Sundry complications such as infection and the mutilation resulting from radical surgery have been encountered. The presenting symptoms have been more severe and relief has been less easily accomplished. While most of these women can be included in the group suffering from premenstrual distress, some of the clinical pictures were atypical, requiring the therapeutic test for their diagnosis.

As one listens to the histories of a larger number of these women, one's conviction grows that their functional disorders, varied and diverse though they may be, are all parts of one clinical complex and attributable to a common cause. Thus, the women who complained of headache, which might range in intensity from a dull discomfort to a blazing migraine, were found on questioning to have more or less digestive disturbance as well. Those whose chief woe was "nervousness," running all the way from an irritable grouch to a week of weeping, had also some headache, and so on. The pattern varied with individuals and the individual pattern varied from time to time, yet all the patients had something in common. Freed's [5] suggestion that the entire complex be given the comprehensive name of premenstrual distress has merit.

Materials and Methods

Synapoidin (Parke, Davis & Co.) is a "gonadotropic preparation . . . obtained by combining chorionic gonadotropin (Antuitrin-S) with gonadotropic hormone extracted directly from the anterior pituitary." It has been shown that in laboratory animals "the combined hormones as contained in Synapoidin have a gonad-stimulating effect several fold greater than the components administered separately." The preparation is standardized in "Synergy Rat Units," based on the minimal dose required to produce a five-fold increase in the ovarian weight of sexually immature female rats. As marketed, it contains 15 such units to the c.c.

Several other preparations of gonadotropin were tried in approximately parallel dilutions. Any of these gonadotropins may, in an occasional subject, induce a blanching of the skin at the site of injection. Perhaps this is caused by the presence of a trace of posterior pituitary in the extract. This blanching soon disappears and it has no clinical significance, although it may retard the appearance of a positive reaction. This effect was observed less frequently with Synapoidin, which also elicited stronger and more uniform reactions. For these reasons its use has been continued.

The active allergen appears to reside in the anterior pituitary hormone or in its combination with chorionic gonadotropin. Antuitrin-S, the chorionic component, was used as a control on 25 women who reacted positively to Synapoidin. Only two relatively weak positive reactions occurred, and no further tests were made with Antuitrin-S. This resembles the experience of Zondek and Bromberg, who mention encountering only "one case of sensitivity toward chorionic gonadotropin." They used Korotrin (Winthrop).

Dosage

Synapoidin in 1:5 dilution was used throughout this series. Where doses are stated, this dilution is to be implied. The initial dose was always that of the positive test, 0.02 c.c. No patients were treated who did not react positively and definitely to this test. Because of experience gained in the earlier work, in every case the attempt was made to adjust the dosage to the individual's requirement as determined clinically, and *no attempt was made to increase the dose beyond the quantity needed to produce symptomatic relief*. In only two cases was the maximum dose of 0.30 c.c. exceeded. It was observed that older women generally tolerated and required a larger dose than their juniors.

As a rule two doses were given in each menstrual month, the first about one week after bleeding ceased, the second a week later. When menses were irregular or delayed, one dose a week was administered until the normal period was reëstablished.

All injections were strictly intradermal.

Results of Treatment

In all, and counting the pioneer case, 107 women showing evidence of sensitivity to gonadotropins by intradermal test have been observed and treated for periods ranging from three months to three years. In the series of 81 additional cases that constitute the material of the present report, the results were as follows:

1. *Premenstrual distress.* These women, constituting some 60 per cent of the case material, presented the syndrome of premenstrual tension and headache with its concomitants in varying combinations and degrees of intensity. Most of them had other allergies. Serious organic complications were unusual. The greater number had not sought medical relief from their discomfort, believing that nothing could be done about it; the few who had seemed to hold a like opinion.

Total cases, 49. Relieved, 33; improved, 9; unimproved, 6; not treated, 1. Average dose, 0.09 c.c. twice monthly.

Comment: In this group there was ready response to treatment. When relief was attained and continued over a few periods, it continued for several months without further gonadotropic medication.

2. *Premenopausal group.* These were women who had experienced a sharp increase of their allergic symptoms at the approach of the climacteric. With one exception they were asthmatic. None had as yet manifested the vascular and nervous indications of the menopause. All had received estrogenic medication without relief. Treatment directed toward their known allergies, formerly not without success, no longer controlled their symptoms. Essentially the same treatment supplemented by a suitable dosage of gonadotropin brought about substantial improvement in the majority of the cases. In two instances, it made the difference between invalidism and a nearly normal mode of living.

Total cases, 10. Relieved, 4; improved, 4; unimproved, 2. The dose varied widely, from 0.03 to 0.30 c.c.

Comment: Because of their age, the presence of complications and the existence of irreversible organic damage, the treatment of this group was difficult. Some of them required and tolerated a relatively large dose. This raises the question of whether the beneficial effect was due to ovarian stimulation, rather than to a specific desensitizing action. This will be discussed later.

3. *Prepubertal.* A girl, aged 12 years, whose chronic asthma had gone out of control as puberty approached was promptly relieved when 0.05 c.c. of diluted Synapoidin was added to her regular treatment at weekly intervals. Normal and uneventful menstruation began two and one-half months later.

Comment: There was a girl with a similar history in the series reported earlier.

4. Acniform facial eruption, during the premenstrual week; four cases. Three school girls, who also had hay fever, were improved; one had permanent relief without scarring. Their average dose was 0.15 c.c. A woman of 38 years, with a similar eruption modified by roentgen-ray, was not benefited by a full dose of gonadotropin, supplemented by vaccine and staphylococcus toxoid.

Note: These girls were sternly enjoined to stop pricking and squeezing their pimples.

5. *Urticaria*, and an undiagnosed condition. There were three cases of urticaria, all referred. All were found, when they could be tested, to react positively to Synapoidin; no other positive reactions could be demonstrated. All recovered in time, but the effect of the gonadotropin therapy is doubtful. The dosage varied from 0.12 to 0.30 c.c. The fourth patient in this group, reported as a medical curiosity, could not be diagnosed by the several doctors who examined her.

Case 1. Mrs. M. M., aged 24 years, referred by Dr. W. H. Woern, had always been healthy, and her periods were normal. Her only complaint was that for several years she had been annoyed at times by nasal stuffiness and a running nose, and this was not affected by place or season. Her present illness had begun abruptly three days before her menstrual period with what she thought was a feverish cold. Next morning her face began to swell, and in a few days the swelling involved the neck and

the extremities. She thought that she had sinus infection, but Dr. Woern found no evidence of it; instead, the nasal mucosa was edematous and irritable, and the usual local applications made it worse. She was referred for diagnosis and treatment.

She looked like a person with nephrosis, but she was not sick. Other than a moderate eosinophilia, laboratory tests revealed nothing abnormal. An elastic swelling that did not itch involved the face so that she could hardly see out of her eyes. On the neck and extremities it was of lesser degree. The rest of her skin was clear.

She was doing war work while her husband was overseas. Patch tests with the usual substances, plus dusts and chemicals from her place of employment, were negative. The routine tests with allergens were also negative by intradermal injection; the only positive test was to diluted Synapoidin. This was given twice a week, in a dose that finally reached 0.40 c.c., more than any other patient in this series tolerated. The edema gradually subsided, and after five weeks, during which treatment was interrupted by a normal menstrual period, the swelling disappeared. Treatment was stopped, and next month there was a mild recurrence of symptoms, which subsided after two doses. A year later, a follow-up letter reported no further trouble. Her husband was home from the wars. Again, the effect of treatment is in doubt.

6. *Dysfunctional bleeding*, with irregularity of menstrual time. Three cases, one so serious that hysterectomy was about to be done. All were relieved and normal menstruation at 28 day intervals was restored. All these women have other allergies. Average dose, 0.20 c.c., two or three times monthly, continued until relief.

7. *Vicarious menstruation.* One case, Mrs. C., a divorcee, aged 29 years, nullipara, had come to Arizona with moderately advanced tuberculosis. In due course her disease was apparently arrested, but she had been kept on the rest cure for a year longer because of irregularly recurring episodes of hemoptysis. She had no other signs or symptoms of tuberculous activity.

Inquiry disclosed that in her home state, but not in Arizona, she suffered from hay fever. Her family history showed allergic disease. Her menses had begun when she was only 10 years old; the periods had been irregular, and always preceded by several days of malaise and distress. She said that the only way she could tell when a period was coming was by the preliminary sickness. When tested, she reacted positively to eastern pollens and to Synapoidin. The latter was used in 0.20 c.c. doses once a week. After four doses an uneventful menstruation occurred, and the same dose was administered once a month thereafter. For the first time in her life, this woman's menstrual periods were regular and normal. Gradually she resumed her usual mode of life. The improvement in her general health was striking. No further hemoptysis occurred.

8. *Perennial allergic rhinitis* with premenstrual exacerbation. Nine cases, all referred by specialists in diseases of the nose and throat. On routine testing, seven reacted only to Synapoidin; two were sensitized also to house dust.

Results: Relieved, 4; improved, 4; unimproved, 1. Average dose 0.16 c.c.

Comment: Evaluation of the results of therapy in this group is impossible. All had failed to obtain more than transient relief from local treatment, and it was discontinued for the period of observation. All were advised to quit using nose drops. All received Synapoidin in medium dosage twice in the intermenstrual interval. The two who reacted to house dust got that as well, and the others were given intradermal doses of a stock vaccine to which they reacted sharply. While most of them reported considerable relief, the rôle of gonadotropins, either in etiology or in therapy, is open to question.

Psychic Influences

It is well known that emotions may alter the functions of the adrenals and the thyroid; it is reasonable to assume that other endocrine glands can be similarly affected. This may have happened in some of the cases here reviewed. For example, among the failures in group 1, there were two badly adjusted old maids; another woman hinted that her marital life was unsatisfactory. One of the three urticarias (group 5) was distracted by the loss of a baby, another had recently left her husband, or vice versa. Psychic states such as these, if they modify in quantity or quality the endocrine secretions, may have had some effect on the incidence of symptoms and the results of treatment. One woman was turned over to a psychiatrist when the examination was completed; perhaps this should have been done with a few others. In my experience it is most useful to take the patient's history personally. The examiner becomes acquainted with the patient and her individual attitude and problem; the patient acquires confidence in her physician. The psychic factor is bound to be active, and it had better be made to operate in a helpful way. Aside from this simple procedure no attempt at psychotherapy was made. In fact, the management was designed to minimize the effect of suggestion, so far as that can be done when any treatment is used.

Discussion

This paper is a record of clinical observations in private practice. Only the initial case, reported earlier, was thoroughly worked up. In that case the postulates were satisfied and it can be asserted that the patient was allergically sensitized to a preparation of gonadotropins. It would not have been proper to burden the succession of apparently similar patients with the considerable expense of laboratory work necessary for scientific proof.

No series of controls is presented; Synapoidin was not administered in parallel dosage to an equal number of allergic females who reacted negatively to the skin test, although such were readily available. Because of the delicate balance of the menstrual mechanism, such use of a potent gonadotropin was considered unjustifiable. Also, there was the theoretical possibility that sensitivity to the hormone might be induced in persons not previously so afflicted.

The word "desensitization" is purposely avoided in this article. Early in this study it was learned that desensitization, in the sense of inducing tolerance to a large dose by means of a series of steadily increased preceding doses, is neither necessary nor desirable. The effect of the hormone in overstimulating the ovaries soon appears, in the form of lower abdominal pain, engorgement of the breasts and disturbance of the menstrual flow. Injection into the skin, a shock organ, is serviceable in keeping the dosage low. With this technic it is possible to obtain protection against an offending allergen with a fraction of the quantity required by other methods of administration. This statement is based on the author's long experience with intradermal pollen therapy. Incidentally, Zondek's [4] successful treatment of pruritus vulvae by the inunction of minute doses of estrogen applies the same principle. What has been said before is repeated for emphasis: *The best results were obtained by a low dosage, adjusted to the individual's tolerance and requirement, and not increased beyond the point at which relief occurred.*

Up to a certain point which varies with the individual, the endocrine product here discussed behaves exactly like any other allergen in a sensitized subject. The local reaction is the same; it is easy to produce constitutional reaction in its varying degrees. With larger doses the effect may be that of hormone overdose, and the threshold levels of these two intolerances are not the same. When the dosage is kept safely within tolerance, this dual quality is again apparent. For example, the premenstrual exacerbation of an ailment commonly recognized as allergic is prevented, and so is the syndrome of premenstrual distress, which many believe to have an endocrine origin. In the many successful cases there appeared to be a restoration of the balance between the gonadotropic hormones and their natural physiologic antagonists. The women reported not only relief but a notable improvement in their general health. And when this desirable result was obtained, it persisted for several months without further medication in cases of simple premenstrual distress with associated allergies. This was accomplished with an average dose of about one-third of what the manufacturer calls a Synergy Rat Unit, or from 2 to 4 per cent of the recommended intramuscular dose. The positive skin reaction must have some significance. The available evidence warrants no conclusions, but it does suggest certain questions. For example, does intradermal administration, which amplifies the effect of allergens, likewise increase the potency of hormones? Are women who are clinically sensitized to endocrine products also over-sensitive to the hormonal effect of those same products? And might it be possible that premenstrual distress is a localized allergic manifestation, with capillary permeability and edema, like hives? Problems of this sort must be left to those specially qualified and equipped for research.

The results in this series are generally parallel to those obtained by Zondek with steroids in oil, and by Freed and others who used androgens as antagonists of estrogen. These similar results reached by differing

modes of therapy are not incompatible; probably they represent different avenues of approach to the complex reactions of the reproductive cycle. It would seem that the gynecologists, with the choice of three successful methods of treatment, are now in a position to make a substantial subtraction from the sum total of human misery. The allergists, if so inclined, can easily verify or disprove the existence of sensitivity to combined gonadotropins by including a 1:5 dilution of Synapoidin in their test sets. Also, if the dosage is kept below the tolerance limit of the individual patient, they should have no trouble in duplicating the favorable results. It is my firm conviction that women sensitized to gonadotropin respond better to treatment for other allergies when the hormone sensitivity is controlled. Even if this were not true, the physician would be well rewarded by the spontaneous expressions of gratitude on the part of the patients and their families. Apparently the correction of disturbed menstrual function is of more importance than some of us have realized.

Summary

The author's earlier publications on this subject are reviewed. The first [2] reported allergic shock caused by Synapoidin in a patient who later was proved to be sensitized to that gonadotropic preparation. The second [3] was the preliminary report of the symptoms and treatment of 25 women screened out of an allergic clientele by positive reaction to intradermal testing with combined gonadotropins. The results of treatment were encouraging.

This communication is based on the records of 81 cases similarly selected. While the greater number suffered from premenstrual distress together with various allergic ailments, asthma being the commonest, the clinical manifestations of others were different and sometimes atypical.

The method of test and treatment has remained unchanged. Synapoidin (Parke, Davis & Co.) in 1:5 dilution was used in test and treatment. The test was 0.02 c.c. intradermally. Only those women who showed a definite immediate positive reaction were treated.

Desensitization, in the sense of inducing tolerance to a large dose by means of a series of ascending doses, was found to be neither necessary nor practicable. The best results were obtained by a low dosage, adjusted to the individual's tolerance and requirement and not increased beyond the point at which relief occurred.

The results of treatment were good in premenstrual distress; favorable in the premenopausal group; excellent in dysfunctional bleeding; fair in a few cases of premenstrual acne; inconclusive in perennial allergic rhinitis; doubtful in urticaria, and poor in the presence of anxiety states and neurosis.

In favorable cases a dual effect was observed. Premenstrual exacerbation of recognized allergic disease, such as asthma, was prevented and the syndrome of premenstrual distress was likewise abolished. Once esta-

blished, this relief persisted for months without further medication with gonadotropins.

Women clinically sensitized to gonadotropins responded better to treatment for their ordinary allergies when the hormone sensitivity was controlled. Even in the fractional doses employed, the gonad-stimulating effect of Synapoidin was occasionally observed, but in most cases its clinical behavior was that of an allergen.

BIBLIOGRAPHY

1. Finch, J. W.: Etiology of nausea and vomiting of pregnancy, Jr. Am. Med. Assoc., 1938, cxi, 1368–1370. Nausea and vomiting of pregnancy due to allergic reaction, Am. Jr. Obst. and Gynec., 1940, xl, 1029.
2. Phillips, E. W.: Allergic shock caused by Synapoidin, Am. Jr. Obst. and Gynec., 1942, xliv, 706–708.
3. Phillips, E. W.: Relief of allergic premenstrual headache, Southwest. Med., 1943, June, 144–147.
4. Zondek, B., and Bromberg, Y. M.: Endocrine allergy, Jr. Allerg., 1945, xvi, 1–16.
5. Freed, S. C.: Treatment of premenstrual distress, Jr. Am. Med. Assoc., 1945, cxxvii, 377–379.
6. Waldbott, G. L.: Is there an intrinsic asthma? Ann. Int. Med., 1947, xxvi, 863–872.

OBSERVATIONS ON RELAPSES IN PERNICIOUS ANEMIA *

By Edgar Jones, M.D., F.A.C.P., Clifford C. Tillman, M.D., and William J. Darby, M.D., *Nashville, Tennessee*

In the fall of 1945 and winter of 1946 liver extract was discontinued on 12 patients with pernicious anemia who were attending the out-patient department of Vanderbilt University Hospital. There were seven males and five females in the group. Two of the men were Negroes. None had evidence of neurological disease. All of these patients were regarded as being adequately treated. The total amount of liver extract which had been injected during the year prior to withdrawal of treatment varied from 420 to 1020 units and had been given at intervals of three to four weeks in the majority of instances.

The average of red blood cell counts made during the year before treatment was discontinued was 4.74 million for the seven men and 4.29 million for the five women. It is to be noted that two of the women averaged a scant 4 million red cells during this period, at times having counts as low as 3.61 million. One of these patients had been given 50 units of liver extract parenterally every two weeks over a period of three years without causing any red cell increase. Thus it is to be assumed that her "normal" level was at 4 million red blood cells or less. No evidence of infection or other disorders known to inhibit response to liver extract was apparent in either of these patients. It is well to recognize that such patients may be encountered during the assay of hemopoietic fractions. In view of the variability of maximum levels under adequate therapy, what red blood cell level is to be taken as indicating relapse? Strauss and Pohle [1] defined hematologic relapse as occurring when two successive red cell counts were 4 million or less. By such standards our two patients mentioned never had gone beyond the relapse range, in spite of very large doses of liver extract. Rather than set any absolute level of red blood cells it appeared to us better to relate relapse to the red cell levels of the individual patient. Obviously a fall in red cell count to 4.0 million has a different significance for a patient with a treatment level of 5.5 million than for one with 4.5 million. We calculated the mean and standard deviation of counts on each individual patient for the last year of liver therapy. Two successive counts on a patient more than two standard deviations below his treatment mean was defined as a relapse. This procedure makes it highly unlikely that the lower counts were due to chance variation and allows each patient to set his own "relapse level" in relation to his previously maintained values.

* Presented at the Twenty-Ninth Annual Session of the American College of Physicians, San Francisco, California, April 20, 1948.
This work was supported in part by a grant from National Vitamin Foundation, Inc.

By applying these criteria six of the 12 patients had relapsed by April of 1948. Of the seven males five have relapsed; one of the five women. The time required for relapse varied from eight to 18 months. Three of the patients showing hematologic relapse recovered their blood values spontaneously for a few months, only to have a progressive relapse follow. The time of the first relapse is used in this report. This is illustrated in charts 1 and 2.

The six patients who have not relapsed have been from 26 to 29 months without liver extract. Chart 3 shows the course followed by a patient who did not relapse. None of the entire group of 12, whether relapsed or not, has developed complaints of any sort. All have been followed closely with examinations for evidence of neurological disease, glossitis and diarrhea as well as to their general sense of well being. There have been no changes in weight of significance except for one man of the relapse group who has gained appreciable weight. This long period required for relapse emphasizes the caution required in interpreting the maintenance efficacy of an agent substituted for liver extract, e.g. pteroylglutamic acid (folic acid, PGA).

After this relapse program had been under way for about 21 months it occurred to us that it would be of interest to follow the fecal urobilinogen levels of this group. It has been well established [2] that urobilinogen is considerably increased in the stools of patients with pernicious anemia in relapse

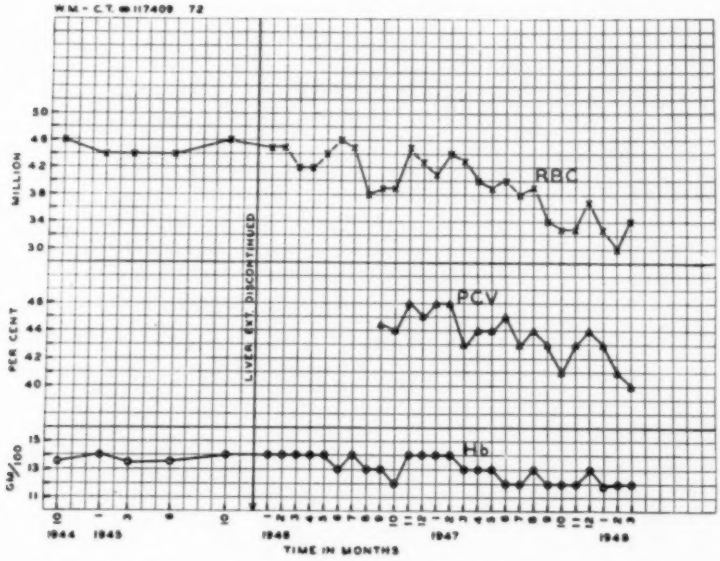


CHART 1. Shows pattern of relapse with a short return to normal levels.

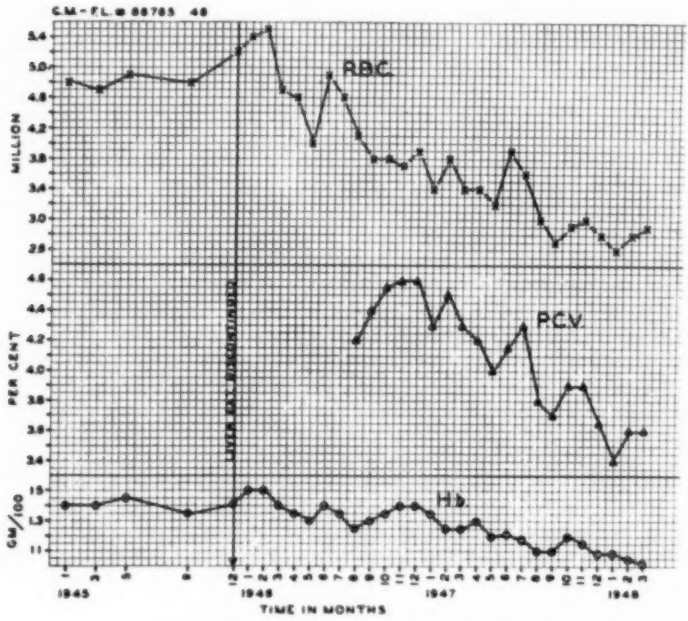


CHART 2. Same pattern of relapse as in chart 1.

and that there is a rapid decrease following the giving of liver and liver extracts. It has also been shown that normal values for urobilinogen are found where there is no anemia.

Fecal urobilinogen was determined by the method of Watson.[3] The majority of determinations were made on stool specimens collected over a period of four days. However, some determinations were made on single stool specimens. We consider single specimens of equal value to four day collections for this purpose since our experience gave us no reason to feel that values of significance were missed by this procedure. Urobilinogen values greater than 300 Ehrlich units per 100 grams of feces were taken to indicate an increase over normal.

Chart 4 shows the relationship between red cell and urobilinogen values. It is to be noted that only where there is anemia is there an increased urobilinogen value.

Chart 5 shows the hematologic course of a man with pernicious anemia who had a good response to parenteral liver extract. He was then allowed to relapse. At this point he was given pteroic acid (chart 6), a part of the pteroylglutamic acid molecule. He obtained an incomplete hematologic response to this material. He was again allowed to relapse at which time he

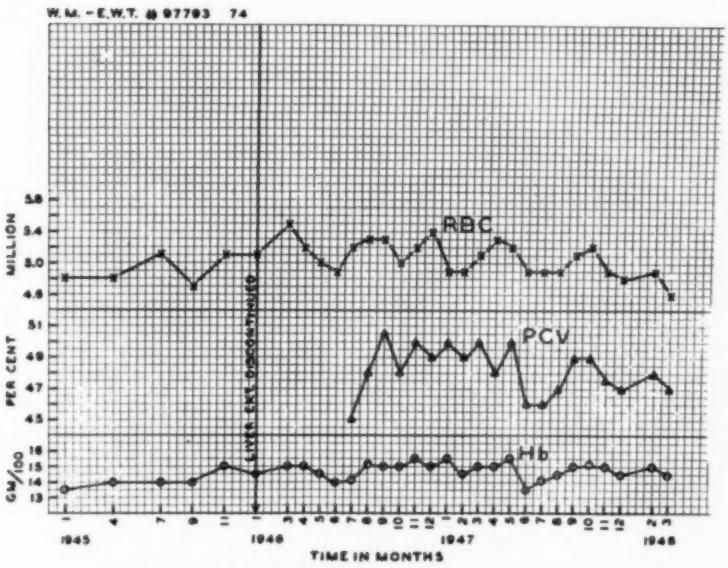


CHART 3. Hematologic findings in a patient who showed no relapse by 26 months.

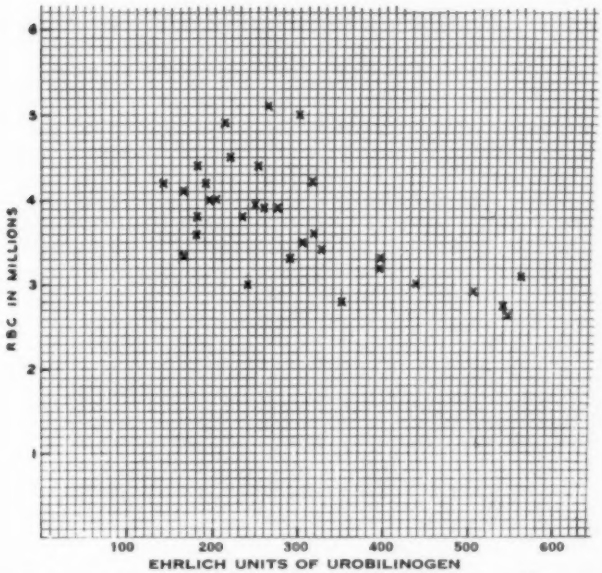


CHART 4. Scatter chart showing relation of red blood cell and urobilinogen levels.

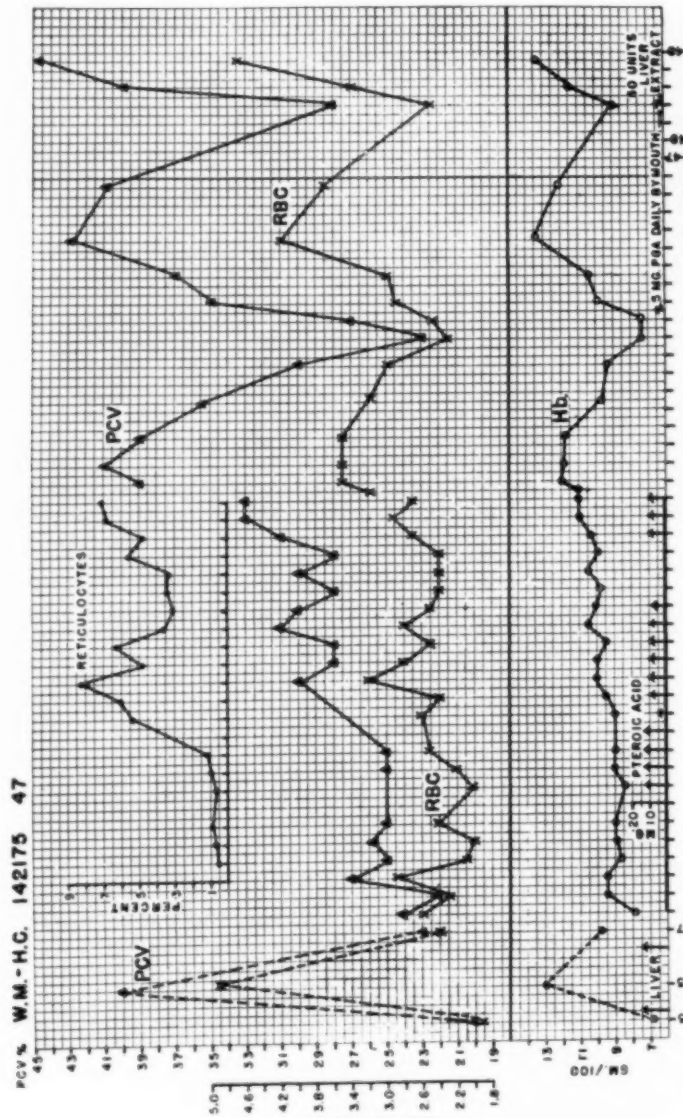
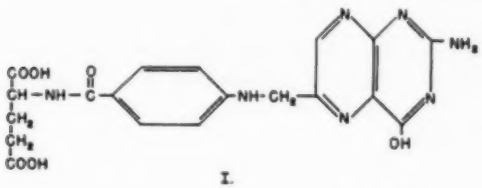
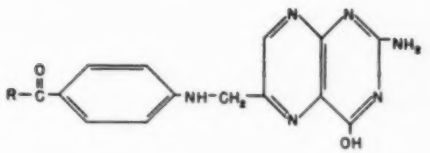


CHART 5. Shows responses of a man with pernicious anemia to liver extract, pteroic acid, folic acid and relapses following cessation of treatment with these materials.



I.



II.

PTEROIC ACID R • OH
FERMENTATION FACTOR R • 3 GLUTAMIC RESIDUES
CONJUGATE R • 7 GLUTAMIC RESIDUES

CHART 6. Formula for pteroylglutamic acid and its constituents.

was given 5 mg. of pteroylglutamic acid by mouth with an initial good response. However, while receiving PGA in 5 mg. doses daily he exhibited a definite relapse. He was then given large doses of liver extract by injection, obtaining the highest blood values seen at any time during the three year period of observation.

DISCUSSION

No cause is apparent for the differences in time required for relapse to occur in the 12 patients observed. Certainly there was no correlation between time of relapse and the amount of liver extract given during the year prior to its withdrawal. It is of interest that of the seven men followed five have relapsed, whereas only one of the five women has relapsed. The small number of patients renders this sex difference probably of no significance. It is of further interest that in three of the patients who showed relapse there was a short-lived return to higher than relapse values before sustained relapse ensued.

No neurological manifestations developed in any of the 12 patients during the period of observation. This is of interest in light of recent reports [4, 5] of a high incidence of neurological findings in patients with pernicious anemia who had been given PGA and tends to confirm the suspicion that this new vitamin actually brings about neurological damage.

While high values of urobilinogen in the stools of patients with pernicious anemia in relapse have been observed regularly, it is worthy of note that these increases are shown to begin at a time of only minimal anemia. This further emphasizes the rôle of hemolysis in the pathogenesis of this disease.

SUMMARY

1. Following withdrawal of liver extract six of 12 patients had failed to show hematologic relapse over a period of 26 to 29 months.

2. Eight to 18 months were required for relapse to appear in the six patients exhibiting this.

3. Standards for hematologic relapse are described which relate relapse to the individual patient's blood level before treatment was stopped.

4. The output of urobilinogen in the stools increases early in hematologic relapse and appears to increase as anemia progresses. This indicates that hemolysis becomes operative early in the relapse of pernicious anemia and emphasizes its importance in the pathogenesis of this disease.

BIBLIOGRAPHY

1. STRAUSS, M. B., and POHLE, F. J.: The duration of remission in pernicious anemia with liver therapy, Jr. Am. Med. Assoc., 1940, cxiv, 1318.
2. FARQUHARSON, R. F., BORSOOK, H., and GOULDING, A. M.: Pigment metabolism and destruction of blood in Addison's (pernicious) anemia, Arch. Int. Med., 1931, xlviii, 1156.
3. WATSON, C. J.: Studies of urobilinogen. 1. An improved method for the quantitative estimation of urobilinogen in urine and feces, Am. Jr. Clin. Path., 1936, vi, 458.
4. HEINLE, R. W., and WELCH, A. D.: Folic acid in pernicious anemia: failure to prevent neurologic relapse, Jr. Am. Med. Assoc., 1947, cxxxiii, 739.
5. ROSS, J. F., BELDING, H., and PAEGEL, B. L.: The development and progression of subacute combined degeneration of the spinal cord in patients with pernicious anemia treated with synthetic pteroylglutamic (folic) acid, Blood, 1948, iii, 68.

THE USE OF A NITROGEN MUSTARD* IN HODGKIN'S DISEASE AND LYMPHOSARCOMA†

By ANDREW H. MEYER, M.D., and W. C. OVERMILLER, M.D.,
Oakland, California

MEDICAL science has profited from the study of agents used in chemical warfare. Investigation into the mode of action of mustard gas revealed a type of action of sulfur and nitrogen mustards which is unlike that of any other chemical agent and resembles in many ways that of roentgen-rays.[1] The effects of the mustards on lymphoid tissue, coupled with the finding that actively proliferating cells are selectively vulnerable to the cytotoxic action of the mustards, led to its use in the treatment of neoplasms of lymphoid tissue. Of the many substances studied, two variants of special importance have emerged: tris (β-chloroethyl) amine hydrochloride and methyl-bis (β-chloroethyl) amine hydrochloride.

This report deals with the therapeutic use of methyl-bis (B-chloroethyl) amine hydrochloride, in two cases of Hodgkin's disease, and three cases of lymphosarcoma.

Dosage and Method of Administration: The amount of the methyl-bis compound recommended as a single course is 0.1 mg. per kilogram intravenously on four successive days (a total of 0.4 mg. per kilogram).[3] Subsequent therapy varies with each patient.[2] In the following cases if the clinical response was not satisfactory after two to three weeks and the hemogram was within normal limits, two to four additional injections of methyl-bis were given. The interval between courses of therapy varied from two to 12 weeks.

Nitrogen mustard must be administered only by the intravenous route, taking great care to prevent extravasation of the solution. The solution is freshly made by adding 10 c.c. of normal saline solution to the sterile glass ampule containing 10 mg. of the dry salt. It is necessary that injection be accomplished within five minutes of preparation of the solution because of the rapid hydrolysis which may occur with consequent loss of efficacy. Pain during injection and subsequent thrombophlebitis of the injected vein were frequently noted by us and others [2] during the direct syringe technic of drug administration. This complication, it was found, could be generally prevented when the calculated dose was injected into the rubber tubing of a freely flowing intravenous infusion of glucose or saline solution.

Toxic Manifestations: These may be classified as early (within 24 hours of medication) and late. The early toxic effects consist of (*a*) pain and

* Methyl-Bis (β-chloroethyl) Amine Hydrochloride.

† Received for publication November 8, 1947.
From Fairmont-Alameda County Hospital, San Leandro, California.
We wish to thank Drs. Louis J. Ruschin and Gerald Crenshaw for allowing us to include their cases.

tender induration at the site of injection if the solution escapes from the vein; (*b*) thrombophlebitis of the vein being used to introduce the medication; (*c*) nausea and vomiting occurring within one to three hours after injection and persisting for from two to 18 hours [4] and (*d*) diarrhea during the course of therapy.[3]

The late toxic manifestations result from widespread destruction of hemopoietic tissue and may be observed in the following sequence: (1) lymphopenia, (2) granulocytopenia, (3) thrombocytopenia and (4) moderate anemia.[2] These serious complications almost invariably occur within the first three weeks and make hemograms a necessity for three weeks following methyl-bis therapy.

In our cases all of these complications were observed to some extent while nausea and vomiting after each injection of medication was universal. Follow-up examinations included urinalyses, cephalin flocculation, thymol turbidity tests, icteric index and plasma proteins with A/G ratio and showed no remarkable change in these patients.

Case Reports

Case 1. A 36 year old white male entered the hospital July 17, 1946, in the terminal stages of Hodgkin's disease. History revealed that he had received repeated roentgen-ray therapy since 1938. In July, 1946, persistent nausea, vomiting, dyspnea, orthopnea and severe pain along the distribution of the right sciatic nerve had developed. Two separate radiological departments felt that further roentgen-ray therapy was not indicated, and he entered Fairmont Hospital for terminal care.

Physical examination revealed a poorly nourished, chronically ill white male in moderate respiratory distress. The temperature was 101° F., pulse 100 and respirations 30 per minute. The blood pressure was 110 mm. of mercury systolic and 90 mm. diastolic. Entrance weight was 120 pounds. Lymph nodes were enlarged bilaterally in the cervical, supraclavicular, axillary and inguinal regions. There was a firm mass 6 by 6 by 2 cm. in the fourth left intercostal space, a mass 6 by 4 cm. in the belly of the left rectus abdominis muscle and a mass 4 by 4 cm. in the right sacral area. The spleen extended to the crest of the left ilium.

Significant laboratory data showed a hemoglobin of 8 grams; roentgenological studies revealed a left hydrothorax, probable pericardial effusion and sclerotic changes in the third lumbar vertebra. Two lymph node biopsies showed the histological picture of Hodgkin's disease.*

Course: Methyl-bis 0.1 mg. per kilogram of body weight per day was given on four consecutive days, beginning August 12, 1946. Each injection was followed by nausea and vomiting, lasting two to four hours. Ten days later all masses had decreased strikingly in size, the appetite was ravenous and the patient was afebrile. However, pain in the distribution of the right sciatic nerve persisted and required aspirin and codeine for relief.

Because of the pain and the gradual reënlargement of the previously described masses, therapy was repeated, beginning September 13. Tumor regression again occurred, but the right sciatic pain became sufficiently severe to require Demerol for relief.

* Interpreted by Dr. R. J. Parsons.

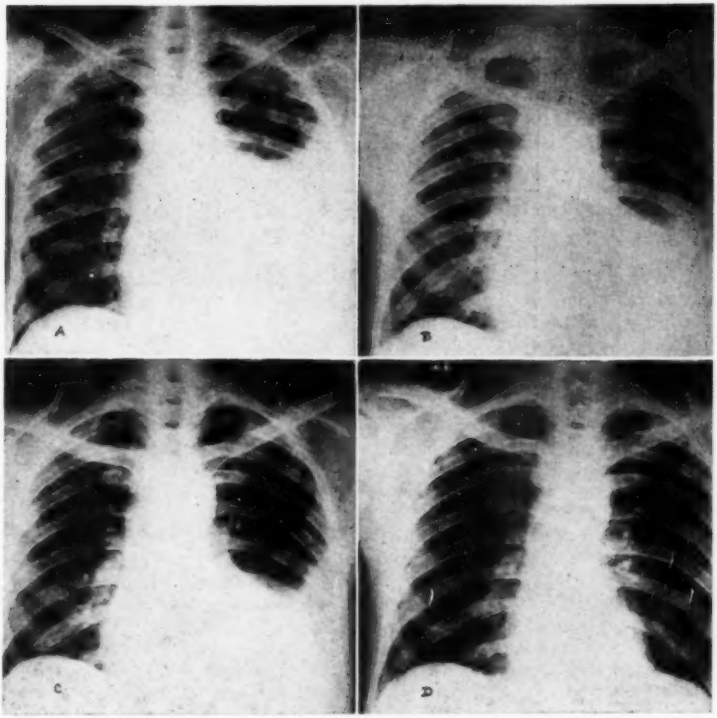


FIG. 1. (Case 1.) Roentgenograms showing effect of therapy on the progress of the mediastinal lesion, pericardial and pleural effusion. "A" represents the pretreatment film. "B" was taken 18 days after first course nitrogen mustard was begun. "C" 30 days after first course nitrogen mustard was begun. "D" 67 days after first course nitrogen mustard, and 35 days after second course. Between July 30, 1946 and October 18, 1947, two courses of the drug were administered.

By October 15, the patient had gained 11 lbs.; a chest roentgenogram was described as normal, but right sciatic pain had increased until it was occasionally necessary to use morphine in addition to Demerol to obtain relief of pain.

A further course of four methyl-bis injections was begun on November 8, and, as no relief was noted, two more injections were given on November 21 and 22. Following this, symptomatic and objective improvement was dramatic; narcotics were discontinued, and the patient discharged to clinic care on December 4, 1946.

Two further courses of methyl-bis were given in January and March, 1947. As of June 1947, the patient has been referred to the roentgen-ray department for therapy to a mass in the left gluteal region. This mass has failed to disappear under methyl-bis therapy. Biopsy of the mass on June 23, 1947 showed extreme fibrosis and numerous cells of the Reed-Sternberg type bordering an area of anemic necrosis. No eosinophiles were found but the lesion was interpreted as a late stage of Hodgkin's disease showing areas of necrosis.* The physical status of the patient allows him to

* Interpreted by Dr. R. J. Parsons.

hold two part-time positions. His weight is 162 lbs. (a gain of 42 lbs.), hemoglobin 16 grams per 100 c.c., and white cell count 6600 per cu. mm. with a slight shift to the left and an eosinophilia of 11 per cent.

Case 2. The patient, a 25 year old white male, first noted undue fatigue and vague chest pains in June, 1945.

Physical examination revealed only moderate bilateral axillary lymphadenopathy. A roentgenogram of the chest was interpreted as showing a widened mediastinal shadow. A lymph node, removed from the left axilla, showed the changes of early Hodgkin's disease.

Course. Roentgen-ray therapy to the mediastinum reduced the width of the mediastinal shadow until October, 1946, when no further response was noted and it was decided to use methyl-bis.

Following the first series of four injections, the mediastinal and axillary nodes slowly regressed in size. A second course of methyl-bis was given in January, 1947. Following each of the courses, lymphopenia and leukopenia were noted, but the count returned to normal within three weeks. As of June, 1947, the patient is symptom-free, shows no recurrence of mediastinal or axillary adenopathy and is gainfully employed.

There have been three cases of histologically proved lymphosarcoma in this group.

Case 1. A 69 year old white female was referred for methyl-bis therapy in October, 1946. Her history revealed that her complaints had been controlled by roentgen-ray therapy since 1941, but at the time of referral skin changes prevented further treatment.

Physical examination showed a chronically ill patient. The axillary and inguinal lymph nodes were enlarged and a basket-ball sized mass was present in the right lower quadrant of the abdomen.

Course. Two weeks following a course of methyl-bis, the patient had a sense of well-being; the peripheral lymph nodes had markedly decreased in size, and the abdominal tumor was no longer palpable. A leukopenia of 1200 cells per cu. mm. developed by the fourteenth day following therapy, but the leukocyte count returned to normal within one month.

A repeat course of methyl-bis was given in January, 1947, following reënlargement of the lymph nodes and reappearance of the abdominal mass. Clinical and hematologic response was similar to that following the first course.

Following each injection of methyl-bis, nausea and vomiting of three to four hours' duration appeared.

As of June, 1947, the patient appears to be in good health, except for radiculitis of the sixth left thoracic nerve.

Case 2. A 51 year old white female was referred for methyl-bis therapy in November, 1946. Her history revealed that she had been receiving roentgen therapy since 1944, but that for the present, skin tolerance had been reached.

Physical examination showed a chronically ill patient with generalized lymphadenopathy. There was 3 plus pitting edema of the left arm and laryngeal stridor.

Course. Following a series of four injections of methyl-bis, beginning November 8, there was marked decrease in the lymphadenopathy, decrease in the edema of the arm and disappearance of the stridor.

A return of the previously described signs and symptoms necessitated a repeat course of methyl-bis beginning December 15. Marked improvement again occurred, but the patient died in her sleep January 12, 1947. No autopsy was obtained.

Case 3. The patient, a 59 year old white female, entered the hospital March 24, 1947. In February, 1946, a nodule had developed in the left anterior triangle of the

neck and had grown rapidly. In May, 1946, a similar nodule appeared on the right side of the neck and enlarged rapidly. Biopsy of a cervical lymph gland was diagnosed as reticulum-cell sarcoma. Roentgen-ray therapy from July, 1946, through February, 1947, only partially controlled the size of the cervical nodes.

In January, 1947, the patient developed a peripheral facial weakness on the left and experienced difficulty in talking and breathing. At this time she also complained of severe pain in the left side of the neck and face.

Physical examination revealed a chronically ill white woman. The notable physical findings were a firm mass extending from beneath the angle of the left mandible forward to the left submental region. The right submaxillary area contained a firm mass the size of a baseball. The liver was palpable three fingers'-breadth below the costal margin and was smooth to palpation.

Course. A series of four daily injections of methyl-bis, begun March 4, 1947, resulted in marked relief from pain and a striking decrease in the size of the cervical lymph glands. However, only a slight decrease in the dysphagia and vomiting was noted.

The cervical glands remained small, relief from pain continued but marked dysphagia and vomiting returned a week after the course of methyl-bis was completed. Our supply of methyl-bis did not allow us to repeat the treatment. The patient died on April 13, 1947.

Gross Autopsy. No palpable cervical or axillary masses and no evidence of metastases to the lungs was noted. The liver showed two small tumor nodules and one nodule measuring 4 by 3 cm. A calculus, one centimeter in diameter, was impacted at the junction of the cystic and common bile ducts. Both kidneys showed diffuse neoplastic infiltrations.

Microscopic Examination. A section from a liver nodule was interpreted by Dr. R. J. Parsons as "lymphoblastoma, of large cell type, or a lymphosarcoma."

Summary

Two cases of Hodgkin's disease, treated with nitrogen mustard, methyl-bis (β-chloroethyl) amine hydrochloride, have responded favorably at a period when further roentgen-ray therapy was not considered advisable. The two living cases are pursuing gainful lives 10 months and eight months after initial methyl-bis therapy. The case which has been followed for 10 months is now receiving roentgen-ray therapy to an area of local recurrence.

Of the three cases of lymphosarcoma, treated after further roentgen-ray therapy was not deemed advisable, one is leading a useful home life eight months after initial therapy; one received marked subjective and objective relief but died in her sleep one month after the last course of therapy, and the third experienced considerable relief from pain, disappearance of peripheral lymphadenopathy, but no relief from dysphagia or vomiting. Autopsy revealed metastatic tumor nodules in the liver and kidneys.

Conclusions

The position which methyl-bis (β-chloroethyl) amine hydrochloride will take in the treatment of Hodgkin's disease and lymphosarcoma is, as yet, undetermined. However, the fact that it is effective palliatively, in certain instances of these diseases, is apparent.

It is our plan at present to use roentgen-ray therapy to tolerance in both Hodgkin's disease and lymphosarcoma. The nitrogen mustards will be used when further radiation therapy is not available. As in our Case 1, local recurrences will be treated by x-radiation, if possible.

BIBLIOGRAPHY

1. GILMAN, A., and PHILIPS, F. S.: The biological actions and therapeutic applications of the β-chloroethyl amines and sulfides, Science, 1946, ciii, 409–414.
2. GOODMAN, L. S., WINTROBE, M. M., DAMESHEK, W., GOODMAN, M. J., GILMAN, A., and MCLENNAN, M. T.: Nitrogen mustard therapy, Jr. Am. Med. Assoc., 1946, cxxxii, 126–132.
3. JACOBSON, L. O., SPUR, C. L., BARRON, E. S., GUZMAN, S. T., LUSHBAUGH, C., and SICK, G. F.: Nitrogen mustard therapy, Jr. Am. Med. Assoc., 1946, cxxxii, 263–271.
4. RHODES, C. P.: Nitrogen mustards in the treatment of neoplastic disease, Jr. Am. Med. Assoc., 1946, cxxxi, 656–658.

THE USE OF THE EXERCISE TEST IN THE DIAGNOSIS OF CORONARY INSUFFICIENCY *

MILTON GROSSMAN, M.D.,† WILLIAM W. WEINSTEIN, M.D.,‡ and LOUIS N. KATZ, M.D., F.A.C.P., *Chicago, Illinois*

THE differential diagnosis of precordial pain may present a difficult problem. It is for this reason that the electrocardiogram has recently gained such wide vogue. However, it is now apparent that a normal electrocardiogram does not necessarily exclude coronary disease and it is becoming clearer that other diseases can lead to electrocardiographic changes which may imitate coronary patterns. A need has developed for some tests to measure the adequacy of the coronary circulation. Two such tests are now being used. One is the anoxemia test, the other the exercise test. In both the judgment is based upon the electrocardiographic alteration. They have been widely used recently to confirm or to establish the diagnosis of coronary insufficiency. There is some controversy over which of the two gives more accurate information. The proponents of the anoxemia test claim a slight increase in accuracy of diagnosis,[1, 2] but others have considered the two tests of equal value.[3] It appears to us that if any difference is present, it is probably slight.

On the other hand the question of availability and safety of the test must be considered. The equipment for the exercise test is simple compared to that needed for the anoxemia test. For the exercise test a metronome and a stairs of two steps are all that is needed. The anoxemia test requires tanks of oxygen and nitrogen, a mask, a mixing apparatus or an anesthesia machine. The percentage of significant unfavorable reactions is less with the exercise than with the anoxemia test. With the former, precordial pain, dyspnea and weakness are the main reactions noted and these can be quickly alleviated by stopping the exercise. With the anoxemia test, 100 per cent oxygen may be given for unfavorable reactions. However, with this test not only does precordial pain occur, but headache, cyanosis, anxiety, clonic tremors, marked bradycardia and shock have been reported and these latter reactions have occurred in controls as well as patients suspected of coronary insufficiency.[4, 5, 6, 7] Pulmonary edema, cardiac arrest and even death [8] have occurred with the anoxemia test.

Confusion has arisen in regard to the exercise test because in the literature there has been considerable variability in the amount, type and rate of

* Received for publication December 16, 1947.
From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago, Illinois.
Aided by the A.D. Nast Fund for Cardiovascular Research.
This department is supported in part by the Michael Reese Research Foundation.
† Now in Nashville, Tenn.
‡ Now in Seattle, Wash.

exercise as well as in the criteria employed to determine whether or not the test is abnormal. Master et al.[9] have emphasized the importance of standard amounts and rates of exercise and have established criteria for a "positive" test. These criteria are at variance with other reports in which a similar "2 step test" was also used but in which the amount and rate of exercise was not standardized for the age, weight and sex.[1, 10, 11, 12, 13]

In order to determine the efficacy of the 2 step test as an aid in the diagnosis of doubtful cases of coronary insufficiency we have performed 151 tests. We found, as did others, that while the majority of diagnoses of angina pectoris (coronary insufficiency) can be made from the history, there are some instances in which confirmation was needed. This is particularly true of patients in the younger age group. Often a history compatible with coronary insufficiency is discarded because of the age of the patient. The military services have emphasized that postmortem examinations reveal an unsuspected incidence of coronary disease in the younger individuals.[14, 15]

In the present study we have tried to evaluate the utility of the exercise test for our own guidance and to clarify the criteria by which a normal exercise test can be distinguished from an abnormal one. We were interested also in determining whether this test could be of value as a routine procedure in selected patients. We chose the exercise test, as already mentioned, because of its relative simplicity, the lack of necessity of specialized equipment, the relative freedom from untoward reactions and because it simulates most closely the type of exertion that the individual performs in his daily routine. In this study an attempt was made to use patients whose control electrocardiogram showed no definite evidence of coronary insufficiency. Both those suspected clinically of coronary disease and those who were considered to be normal were included in this series. The patients ranged in age from 15 to 84 years. Included were a number of instances of neurocirculatory asthenia or anxiety neurosis.

Method

In each instance a careful cardiac history and physical examination was performed prior to the test. A clinical impression was made with particular reference to the presence or absence of angina pectoris. The Master "2 step test" was used according to the rules layed down by Master et al.[9] In practically all cases we attempted to perform a double test, i.e., twice the listed number of trips in twice the time. If precordial distress, marked dyspnea or weakness occurred, the test was concluded, noting the number of trips and the elapsed time. In all cases the three standard limb leads and three chest leads (CF_2, CF_4 and CF_5) * were taken. The positions for the chest electrode were marked so that identical points were used throughout the test. A control tracing was taken in all cases prior to the test. After exercise, serial electrocardiograms were taken immediately, and in

* We now use V_2, V_4 and V_5.

two and in 10 minutes. In many of the cases tracings were also taken six minutes after exercise. The limb leads were obtained within 20 seconds following completion of the exercise. The Sanborn (Instomatic) machine was employed to accelerate the shifting from one lead to another. All records were obtained with the patient reclining in bed. The reference point employed for S–T deviations was the isoelectric level (the level at the start of P). When tachycardia developed the P–Q segment was used as the level of reference.

Results

The results of exercise tests in normal individuals emphasize that certain electrocardiographic changes occur following exertion. These are similar to those occurring in patients with coronary insufficiency, but are less in extent. In our series of normal individuals the most significant changes occurred in the S–T segment. Slight fluctuations in T-wave amplitude occur in normal subjects and are not of diagnostic significance. In none of the normal subjects did an upright T-wave become indiscernible or inverted. However, in some normals with inverted T-waves in Lead III and in some who on occasion had an inverted T-wave in CF_2, the T-wave became upright following exercise.

As a result of our analysis, correlated with that in the literature, we have come to the conclusion that in certain cases more than isolated measurements of the S–T depression are necessary for the diagnosis of a positive test. When significant changes did occur they were present in two or more of the six leads. Significant S–T depression, we concluded, was 0.75 mm. or more in a limb lead and 1.50 mm. or more in a chest lead; significant T-wave changes include the appearance of indiscernible, diphasic or inverted T-waves in either Leads I, II, CF_4 or CF_5. We found it valuable not only to look for these particular changes in S–T and T but to judge a test as positive or negative on the basis of the change in contour of the entire S–T–T complex. In our series no specific coronary pattern, of the type seen in acute myocardial infarction, developed following the exercise test, although such have been noted.[16] In one case, however, in which premature systoles developed, the premature systoles showed a coronary pattern in CF_2 diagnostic of a positive test (figure 1). We consider that the development of frequent premature systoles, of intraventricular and A–V block [3] is usually indicative of a positive test.

Although most of our cases of suspected coronary insufficiency employed in the exercise test were patients with normal control electrocardiograms, it is probable that had we used less rigid criteria we would have obtained a greater percentage of positive tests. This is particularly true among the cases listed as doubtfully positive. Many of these latter showed major changes in one lead and minor changes in other leads. It is also likely that we would have obtained a greater percentage of positive tests had we accepted more patients with abnormal electrocardiograms.

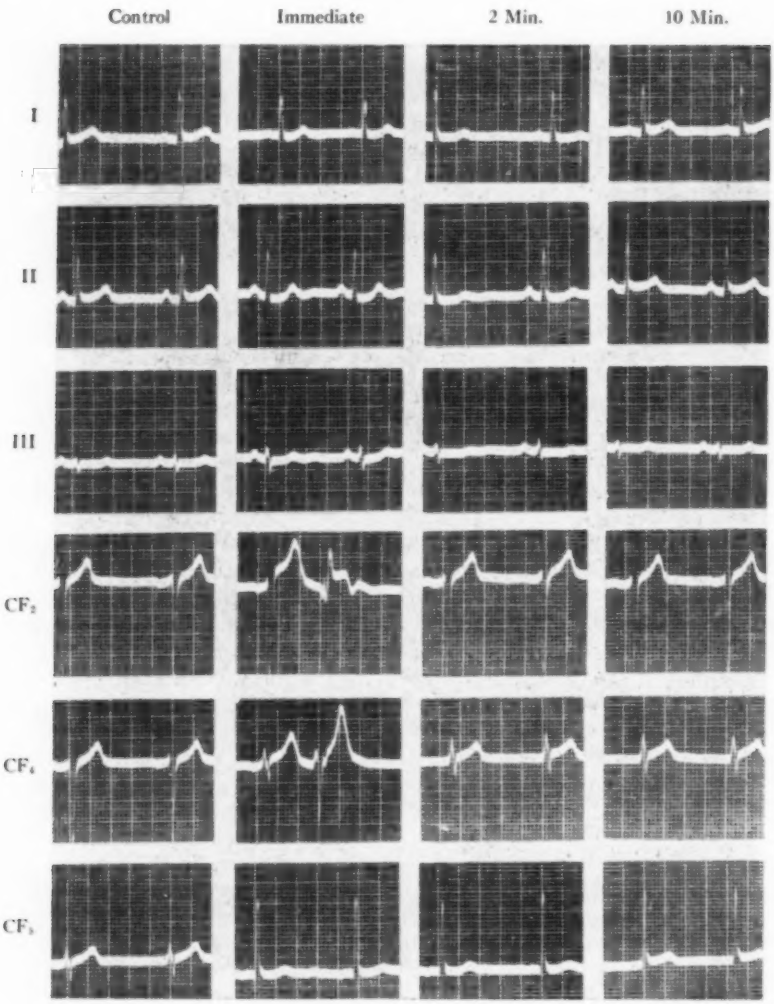


FIG. 1. A positive exercise test showing premature systoles with a coronary contour (in CF_2). The two minute record shows the greatest flattening of the T-waves in the limb leads.

The results in our 151 patients are summarized in tables 1 and 2. Of the 151 patients, 43 gave a history compatible with coronary insufficiency; of these 43 cases, 22 had positive tests, four were doubtful and 17 were negative. In the remaining 108 patients the history was not suggestive of

TABLE I

Evaluation of Exercise Test on Basis of History, Symptoms during Test, Appearance of Control Electrocardiogram and Physical Findings of Heart Disease

		Exercise Test in Patients With						Exercise Test in Patients Who					
		History Suggestive of Angina Pectoris			History Negative for Angina Pectoris			Developed Precordial Distress, Dyspnea or Weakness During Test			Did Not Develop Precordial Distress, Dyspnea or Weakness During Test		
		Pos.*	Doubt.*	Neg.*	Pos.*	Doubt.*	Neg.*	Pos.*	Doubt.*	Neg.*	Pos.*	Doubt.*	Neg.*
Normal resting ECG	Without objective evidence of heart disease	13	0	5	2	2	76	11	7	7	4	2	74
	With heart disease	1	1	3	0	0	3	1	1	2	0	0	4
Abnormal resting ECG (no evidence of chronic coronary insufficiency)	Without objective evidence of heart disease	2	0	2	2	0	9	2	0	1	2	0	10
	With heart disease	6	3	7	3	1	10	7	2	4	2	2	13

108 controls—7 Pos., 3 Doubt.
43 non-controls—22 Pos., 4 Doubt.
* Pos. indicates positive test, Doubt., a doubtful test, Neg., a negative test.

TABLE II

Correlation of Symptoms Occurring during Test with Electrocardiographic Test and Clinical Evaluation

	History of Coronary Insufficiency	No History of Coronary Insufficiency
Test positive, symptoms during test positive	18	3
Test negative, symptoms during test negative	11	90
Test positive, symptoms during test negative	4	4
Test negative, symptoms during test positive	6	8
Test doubtful, symptoms during test positive	3	0
Test doubtful, symptoms during test negative	1	3
Totals	43	108

coronary insufficiency; 83 of these 108 cases had normal electrocardiograms and in 79 of them the test was negative. However, in this group there were two positive and two doubtful tests. One of the positive tests was in a 37 year old woman who had atypical precordial pain and the other in a 52 year old man who had three episodes of "gnawing chest pain" but otherwise a negative history. These two cases may very well have been classified as clinically suspected coronary insufficiency. Of the 108 cases whose history was not suggestive of coronary insufficiency, 25 had an abnormal control electrocardiogram. In 19 of these the test was negative, in one it was doubtful and in five it was positive. The positive tests were obtained on:

1. A 63 years old diabetic with exertional dyspnea.
2. A 45 year old physician with intraventricular block but no symptoms and signs of heart disease.
3. A 40 year old woman with marked hypertension.
4. A 40 year old man who had recurring premature systoles.
5. A 24 year old woman with a Lutembacher syndrome.

Thus, it is possible that at least in the first four cases the suspicion of coronary insufficiency may be entertained.

It is worthy of note that the proportions of positive tests in the control and suspected coronary insufficiency groups is approximately the same as that reported by Master [9] using a similar exercise test, and by Lévy [4] and Biorck [1] with anoxemia tests.

It is interesting to note that 38 of the 151 patients developed either chest pain, moderate dyspnea, weakness or dizziness during the test. In all instances the symptoms were minor and in every instance cessation of exercise resulted in the disappearance of the symptoms. In table 2 the results of the exercise test are correlated with the occurrence of these symptoms. It will be noted that of 21 patients, in whom a positive test was obtained at the same time that symptoms developed, 18 had a history of coronary insufficiency. On the other hand, of the 101 patients who had a negative test and did not develop symptoms, 90 had a history that was not compatible with coronary insufficiency. It would thus appear that the occurrence of symptoms tends to fortify the estimate based on the electrocardiographic alterations.

Discussion

Electrocardiographic changes following exercise can not be ascribed exclusively to the development of a relatively inadequate coronary flow. Other factors set up by exercise may play a significant rôle. It is notorious that a number of influences exclusive of anoxemia and ischemia lead to depression of the S–T segment and flattening, and even inversion of the T-wave. Thus, Wendkos [17] found such S–T and T-wave changes occurring in normal individuals following change in position. Increased activity of the sympathetic nervous system can produce such changes and patients with neurocirculatory asthenia and anxiety are prone to exhibit them. These patients will often present symptoms referable to the cardiovascular system. Walser [18] showed that mild exertion lowered the T-wave in normal subjects and that strenuous exercise, while at first increasing the height of the T-wave, later diminished it. Furthermore he found that sympathomimetic drugs exaggerated this response while sympatholytic drugs lessened this effect. Chapuis [19] suggested that sympatholytic drugs might be used to distinguish the electrocardiographic changes produced by exercise on the basis of an underlying organic coronary disease from those due to reflex augmentation of adrenergic influences. He employed dihydroergotamine intravenously in the two groups of patients prior to the induction of anoxemia. Wendkos [20] also has used such drugs to differentiate sympathogenic distortions of the T-wave from those due to intrinsic cardiac disease.

Two other accompaniments of exercise are known to influence the electrocardiogram. These are tachycardia and hyperventilation. The S–T depression caused by tachycardia is well known. To a large extent this is due to the increased size of the auricular T-wave (T_A) which leads to a simul-

taneous depression of the P–Q segment. To exclude this factor we have used the level of the P–Q segment as a reference point whenever a tachycardia of moderate degree or more developed. Hyperventilation decreases the CO_2 content of the blood and hypocapnia has been shown to lead to S–T depression and T-wave inversion.[21, 22]

We recognize that these factors as well as the development of relative coronary insufficiency play a rôle in the electrocardiographic criteria used in judging whether an exercise test is positive or negative. The judgment of the test is empirical and is based on a comparison of the electrocardiographic changes in known cases of coronary insufficiency with those in known normal subjects. This is the method employed in our study. We have felt that it is essential to include, besides the positive and negative groups, a class of doubtfully positive tests. We have tried to eliminate other variables such as previous fatigue, recent meals [23, 24] and marked changes in room temperature. Our criteria for the test demand as great or

TABLE III

Criteria Used in Exercise Test

Author	S–T Depression or Elevation	T-Wave Changes	Other Changes
Twiss and Sokolow[10]	1.0 mm. or more in I 1.5 mm. or more in II 1.5 mm. or more in III 2.0 mm. or more in IV	Change from upright to a diphasic or inverted T_1, T_2 or T_4.	
Levan*[12]	0.75 mm. or more depression in any lead	Change from upright to isoelectric or negative T_1, T_2 or T in chest leads. Change from isoelectric to a well-developed T-wave in I and II.	Also consideration of dwarfing of the QRS amplitude.
Maser and Reisinger[11]	0.75 mm. or more in I 1.5 mm. or more in II 0.75 mm. or more in III 1.75 mm. or more in CF_4	Inversion of T-waves in Leads I, II or CF_4.	Low voltage of T-waves in all limb leads.
Master*[2]	0.5 mm. or more in any lead	Change from upright to isoelectric or inverted T. Change from negative to positive T-wave.	Premature beats or significant arrhythmias, widening of QRS, large Q waves, prolongation of P–R interval.
Biorck[1]	Total of 2.0 mm. or more in limb leads 1.5 mm. or more in any lead	Inversion of T_1, or T_2.	Diphasic T_1 with S–T depression of 1.0 mm. or more.
Our present report	0.75 mm. or more in a limb lead 1.50 mm. or more in a chest lead	Change from upright to isoelectric or inverted T. Change from negative to positive T (in Leads I, II, CF_2 and CF_4).	Occurrence of coronary pattern. Significant premature systoles, intraventricular or auriculoventricular block.

* Used isoelectric point (beginning of P-wave) as the reference point for depression and elevation of S-T segment.

greater change from the normal than that employed by any other group using a standardized technic. This is shown in table 3 which compares the criteria used by various investigators.

In the course of this study it was found that the maximum changes in S–T deviation and T-wave amplitude occurred in some instances several

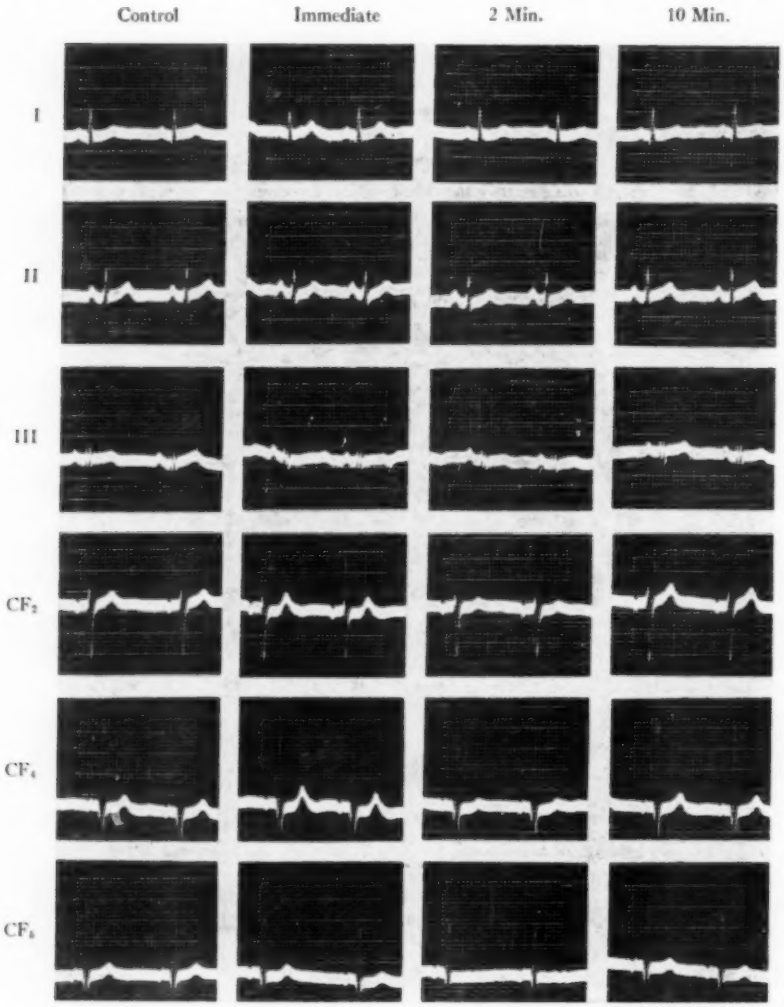


FIG. 2. A positive exercise test in which the maximal changes appear in the record taken two minutes after completion of exercise. Note the marked flattening of the T-waves in the chest leads of the two minute electrocardiogram.

minutes after completion of the test. In two cases, records taken immediately following exercise would have been judged as a negative test while records taken two to six minutes following the exercise showed a positive test (figure 2). It is possible that such "delayed positive" tests might be missed with the anoxemia test since patients may be allowed to breathe 100 per cent oxygen immediately following the period of anoxemia.

It would appear from our experience that the exercise test, when performed by a well-qualified physician with due regard for the safety of the patient, has a definite place in the differential diagnosis of coronary insufficiency. While a negative test does not exclude coronary insufficiency, a positive one fortifies this diagnosis. If liberal standards are employed, false positive tests will be rare. This is not disturbing inasmuch as the exercise test is not the final criterion, but one of a series of evaluations which should lead the clinician to his final judgment. It is obvious that further experience with larger numbers of cases should improve the criteria to be employed in judging the results of the test and thereby should make it more useful in the future. There is no point in using the test when the clinical picture is definite or the resting electrocardiogram shows a coronary contour. There is no point in using the test when there is no suspicion of coronary disease. The real value of the test lies in cases in which the diagnosis is in doubt. However, the test should be employed in known cases of coronary disease and in known normals so that the number of cases from which to build standards can be multiplied. Even with this test great caution should be used when the differential diagnosis is between coronary disease on the one hand and neurocirculatory asthenia and anxiety states on the other.

Summary

1. A standardized exercise test using the Master 2 step stairs was employed in 151 patients, 108 of whom had no history or findings suggestive of coronary insufficiency and 43 of whom had a definite or questionable history or findings of coronary insufficiency. With few exceptions these cases had control electrocardiograms within normal limits. In practically all cases we attempted to perform a double test, i.e., twice the listed number of trips in twice the time set by Master for the given age, sex and weight of the patient.

2. A test was considered positive when there was a significant S–T depression in two or more leads, viz., 0.75 mm. or more in a limb lead and 1.50 mm. or more in a chest lead. A test was also considered positive when the T-wave in Leads I, II, CF_4 or CF_5 became indiscernible, diphasic or inverted. Frequent premature systoles, intraventricular block, A–V block, and the development of a pattern suggestive of myocardial infarction were also considered evidence of a positive test.

3. No diagnostic significance was attached to the development only of an inverted T-wave in Lead III or of T in CF_2 becoming upright following exercise.

4. The correlation of positive tests in the various groups coincided with that reported in previous standardized exercise and anoxemia tests. It was found necessary to include a grouping labelled doubtful positive tests.

5. The development of precordial pain, dyspnea, weakness or dizziness occurred in 38 patients. This was considered supportive evidence of a positive test. When such symptoms occurred the exercise was stopped. In no instance were these symptoms striking.

6. Although a positive test is of diagnostic value (we have not encountered a false positive test in this series), a negative test does not exclude coronary disease.

7. Occasionally the record immediately after exercise is negative or inconclusive only to become positive after a latent period of two to six minutes. It is therefore essential that records be taken at least once during this period.

8. The mechanisms for the development of the electrocardiographic changes are discussed.

9. It is concluded that when properly executed the exercise test is a useful adjuvant in the differential diagnosis of coronary insufficiency.

We are indebted to the house officers of this department for assistance with the test and to physicians of the hospital staff for permitting us to study their patients.

BIBLIOGRAPHY

1. Biorck, G.: Anoxemia and exercise test in the diagnosis of coronary disease, Am. Heart Jr., 1946, xxxii, 689.
2. Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The electrocardiogram during attacks of angina pectoris: its characteristics and diagnostic significance, Am. Heart Jr., 1940, xix, 683.
3. Master, A. M., Nuzie, S., Brown, R. C., and Parkes, R. C., Jr.: The electrocardiogram and the two step exercise: a test of cardiac function and coronary insufficiency, Am. Jr. Med. Sci., 1944, ccvii, 435.
4. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The anoxemia test in the diagnosis of coronary insufficiency, Am. Heart Jr., 1941, xxi, 634.
5. Weintraub, H. J., and Bishop, L. F., Jr.: The anoxemia test for coronary insufficiency, Ann. Int. Med., 1947, xxvi, 741.
6. Pruitt, R. D., Burchell, H. B., and Barnes, A. R.: The anoxia test in the diagnosis of coronary insufficiency, Jr. Am. Med. Assoc., 1945, cxxviii, 839.
7. Biorck, G.: Hypoxemia tests in coronary disease, Brit. Heart Jr., 1946, viii, 17.
8. Levy, R. L.: The anoxemia test as an aid in the diagnosis of coronary insufficiency, Modern Concepts of Cardiovascular Diseases, 1946, xv, No. 4.
9. Master, A. M., Friedman, R., and Dack, S.: The electrocardiogram after standard exercise as a functional test of the heart, Am. Heart Jr., 1942, xxiv, 777.
10. Twiss, A., and Sokolow, M.: Angina pectoris: significant electrocardiographic changes following exercise, Am. Heart Jr., 1942, xxiii, 498.
11. Mazer, M., and Reisinger, J. A.: An electrocardiographic study of cardiac aging based on records at rest and after exercise, Ann. Int. Med., 1944, xxi, 645.
12. Levan, J. B.: Simple exertional electrocardiography as aid in diagnosis of coronary insufficiency, War Med., 1945, vii, 353.

13. Riseman, J., and Stern, B.: A standardized exercise tolerance test for patients with angina pectoris on exertion, Am. Jr. Med. Sci., 1934, clxxxviii, 646.
14. Steigman, F., and Glassner, F.: Acute myocardial infarction in men below forty, Mil. Surg., 1946, xcix, 177.
15. Poe, W. D.: Fatal coronary artery disease in young men, Am. Heart Jr., 1947, xxxiii, 76.
16. Feil, H.: The electrocardiogram of anginal attacks induced by exercise, Modern Concepts of Cardiovascular Disease, 1946, xv, No. 4.
17. Wendkos, M. H.: The influence of autonomic imbalance on the human electrocardiogram, Am. Heart Jr., 1944, xxviii, 549.
18. Walser, A.: Über den Einfluss Vegetativer Pharmaka auf den Ablauf der T-Zacken-Veränderungen im Arbeits-Elektrokardiogramm, Cardiologia, 1946, x, 231.
19. Chapuis, J. P., Jequier-Doge, E., and Wemer, G.: Nouvelles recherches sur l'electrocardiogramme en hypoxemie, Helvet. med. Acta, 1945, xii, 519.
20. Wendkos, M. H., and Logue, R. B.: Unstable T-waves in Leads II and III in persons with neurocirculatory asthenia, Am. Heart Jr., 1946, xxxi, 711.
21. Christensen, B. C.: Variations in the carbon dioxide tension in the arterial blood and the electrocardiogram in man, Acta physiol. Scand., 1946, xii, 389.
22. Thompson, W. P.: The electrocardiogram in the hyperventilation syndrome, Am. Heart Jr., 1943, xxv, 372.
23. Simonson, E., Alexander, H., Henschel, A., and Keys, A.: Effects of meals on the electrocardiogram in the normal subjects, Am. Heart Jr., 1946, xxxii, 202.
24. Gardberg, M., and Olsen, J.: Electrocardiographic changes induced by the taking of food, Am. Heart Jr., 1939, xvii, 725.

THE EFFECT OF CARONAMIDE ON THE BLOOD CONCENTRATION OF PENICILLIN FOLLOWING ORAL AND INTRAMUSCULAR ADMINISTRATION OF PENICILLIN *

By William W. Zeller, M.D., Mark H. Lepper, M.D., Jay A. Robinson, M.D., Harold L. Hirsh, M.D., and Harry F. Dowling, M.D., F.A.C.P., *Washington, D. C.*

One of the greatest problems in the clinical use of penicillin has been the maintenance of adequate plasma concentrations in spite of the rapid rate at which the antibiotic is excreted by the kidneys. Recently Sprague and his associates [1] have developed a drug, caronamide (4′ carboxyphenylmethanesulfonanilide) which inhibits the renal excretion of penicillin. Beyer [2, 3] has postulated that caronamide suppresses penicillin excretion by blocking the specific enzyme system responsible for penicillin transport through the tubular cells. Since it has been demonstrated [2, 4] that of the penicillin excreted about 20 per cent passes into the urine through the glomeruli and 80 per cent through the tubules, the concurrent administration of caronamide and penicillin should theoretically give higher and more prolonged plasma concentrations of penicillin.

Information concerning the chemistry, physiology,[5] pharmacology,[6] toxicology,[7] and early clinical investigation [8] of caronamide has appeared in recent literature. It is the purpose of this paper to present the results we have obtained from the study of the effect of caronamide upon the serum penicillin concentrations in a group of patients treated at the Gallinger Municipal Hospital with varying doses of penicillin and caronamide.

Method of Study

Patients who were receiving penicillin either orally or parenterally were selected for the study, provided they showed no evidence of impaired renal function. In order to evaluate the effect of caronamide, the concentrations of penicillin in the blood were determined following the administration of penicillin alone and then with the same dose of penicillin plus caronamide. Each patient served as his own control for the studies. In order to simulate clinical conditions as nearly as possible, the patients were given penicillin and caronamide for 12 hours or more before blood for penicillin determinations was obtained. The "caronamide bloods" were drawn 24 hours after the "control bloods" at the corresponding hourly intervals in the same patients.

* Received for publication December 20, 1947.
From the George Washington University Medical Division, Gallinger Municipal Hospital, and the Department of Medicine, George Washington University School of Medicine.

Penicillin concentrations in the sera were then assayed using a modification of the Rammelkamp method.[9] *

The results have been tabulated according to a hypothetical fraction, the numerator of which represents the hourly caronamide-penicillin levels and the denominator the hourly control-penicillin levels. The fold increase, or caronamide effect for each of the hours was determined by dividing the caronamide levels by the control levels. An example of this method of tabulation is presented:

	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.
$\frac{\text{caronamide level}}{\text{control level}}$	$\frac{1.25}{.156}$	$\frac{.312}{.078}$	$\frac{.156}{.039}$	$\frac{.078}{.039}$
fold increase $= \frac{\text{caronamide level}}{\text{control level}} =$	8	4	4	2

In order to ascertain the toxicity of caronamide before beginning the study, four patients were given 24 gm. (4 gm. every four hours) per day for seven days. During this period, frequent urinalyses, hemograms, and blood urea nitrogen determinations were obtained. The patients were also observed carefully for any other evidences of toxicity. In an effort to determine the sensitizing effect of caronamide, a second course of the drug was administered to a group of 22 patients seven to fourteen days following an original course of five days, and they were observed particularly for allergic manifestations of drug fever, rash, and conjunctivitis.

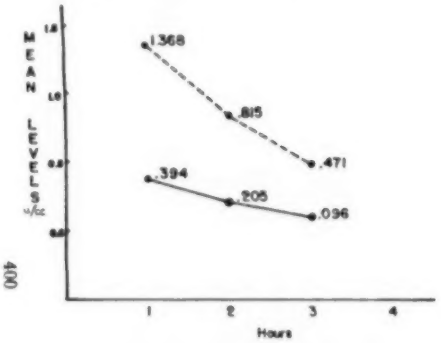
Results

We have administered oral caronamide to 106 patients using varying doses of caronamide and penicillin. Forty of these patients received penicillin by intermittent intramuscular injections. The remaining 66 patients received penicillin by the oral route. The dosage schedules of penicillin most commonly employed were 30,000 units intramuscularly every three hours (26 patients) and 100,000 units every four hours orally (59 patients). These two groups of patients will be referred to hereafter as the *selected intramuscular* or *selected oral series* since statistical evaluation of our results will be concerned chiefly with these groups. When they are considered together, they will be referred to as the *total selected series.*

The mean penicillin serum concentrations and fold increases were calculated for each of the hourly intervals. These mean concentrations for all the patients studied in the *selected series* are shown in figure 1a and for the *selected intramuscular and oral series* in figures 1b and 1c, respectively. It is obvious that caronamide has the ability to increase the concentrations of penicillin in the serum. The statistical significance of the differences between the mean caronamide levels and the mean control penicillin levels was determined according to the method described by Hill.[10] The differences

* A serial two-fold dilution method comparing the inhibition of a test organism by known and unknown amounts of penicillin.

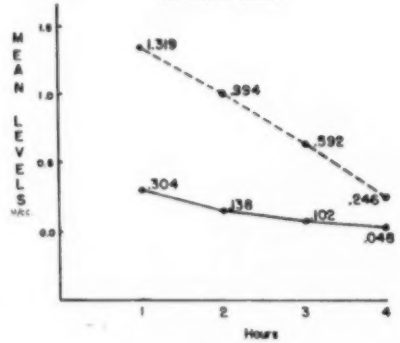
Effect of the oral administration of coronamide on the concentrations of penicillin in the blood following oral and intramuscular administration (Total selected series)



HOUR	t	°F	F.I.
1	5.8	168	3.9
2	3.6	168	3.9
3	2.6	171	4.9

Fig. 1 a.

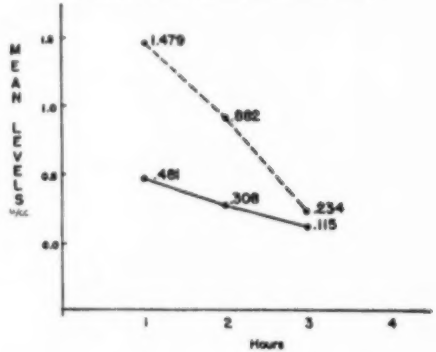
Effect of the oral administration of coronamide on the concentrations of penicillin in the blood following oral administration of 100,000 units every four hours (Selected oral series)



HOUR	t	°F	F.I.
1	4.8	116	4.3
2	4.8	116	7.2
3	3.5	116	5.8
4	1.2*	116	5.1

Fig. 1 b.

Effect of oral administration of coronamide on the concentration of penicillin in the blood following intramuscular administration of 20,000u every 3 hours (Selected intramuscular series)



HOUR	t	°F	F.I.
1	4.0	50	3.0
2	4.0	50	2.8
3	1.1*	53	2.0

Fig. 1 c.

——— Control penicillin curve

– – – – – Coronamide-penicillin curve

t = Value for difference between the means

°F — Total degrees of freedom.

F.I. = Fold increase = $\frac{\text{Mean coronamide level}}{\text{Mean control level}}$

* = Not statistically significant

between the means are highly significant for the *total selected series* and for the *selected intramuscular and oral series* respectively at each of the hours except at the third hour for the *selected intramuscular series* and at the fourth hour for the *selected oral series*.

The average fold increase (caronamide effect) for the *total selected series* is 4.3 with a range from zero to 128 in individual patients. In general, patients not included in the *selected series* had fold increases similar to those in the selected group. Furthermore it can be seen from the figures that the fold increases were fairly uniform for each of the hours. The highest caronamide-penicillin levels, on the other hand, were noted at the first hour and diminished gradually thereafter. The rate of decrement seemed to be fairly constant as indicated by the almost straight line of the caronamide-penicillin curves.

The effect of different dosage schedules of caronamide on a constant dose of penicillin is tabulated in tables 1 and 2. There are no striking differences in the caronamide effect with the various doses of caronamide employed in the series. The mean penicillin concentrations obtained with 3 gm. and 4 gm. of caronamide given every three or four hours respectively, are greater than those obtained with the lower dosage regimens, but the standard deviation from the means is so great that the differences are not statistically significant. That these larger doses have a greater effect than the smaller amounts is suggested, but proof would depend on obtaining similar results in a larger series of patients. The results in the patients who received 2 gm. every two hours do not differ significantly from those in the patients who were given 4 gm. every four hours, but in a larger series the higher means for the latter dosage-schedule might have statistical significance.

When the mean caronamide-penicillin levels obtained with each component series of the *selected intramuscular group* are compared with the mean penicillin levels for the *selected control group*, the differences between the means are significant only at the first hour. The differences between the means for the corresponding figures in the *selected oral series*, on the other hand, are significant at all the hours. In general, the results in the *selected intramuscular series* are not as consistent as those in the *selected oral series*. This variability can be explained by the fact that the former series is smaller than the latter.

Although statistical analysis of the *total selected series* shows significant effect of caronamide for each of the hours, we have observed frequent variation in the response of individual patients. Table 3 shows this variation in response. Approximately 50 per cent of patients failed to show an increase at the fourth hour and did not maintain a serum concentration of penicillin of at least .078 unit per c.c. at this time. Twenty-three per cent of patients had no detectable increase at any one of the hours; 21 per cent had none at two of the hours; 11 per cent had none at three of the hours; and 5 per cent had none at four of the hours. Eight per cent had no response at any of

the hours tested. Patients showing no increase at one or two of the hours for the most part were those who showed no response during the third and/or fourth hours. Forty-nine per cent of patients in the total series maintained levels of .078 unit per c.c. or higher of penicillin continuously for all hours after receiving caronamide as compared with 15 per cent in the

TABLE I

Caronamide Effect for Selected Intramuscular Series 30,000 Units Penicillin Every Three Hours with Varying Doses of Caronamide

Doses of Caronamide	Number of Cases		Versus Own Control			Versus Group Control		
			1 Hr.	2 Hrs.	3 Hrs.	1 Hr.	2 Hrs.	3 Hrs.
2 gm. every four hours	5	CM	1.109	.398	.242	1.109	.398	.285
		CT	.249	.046	.019	.481	.308	.115
		t	2.9	2.4	1.3*	2.3	0.3*	1.5*
		°F	8	8	8	29	29	29
		FI	4.4	8.6	12.7	2.3	1.3	2.5
2 gm. every three hours	7	CM	2.44	.535	.290	2.44	.535	.290
		CT	.535	.577	.150	.481	.308	.115
		t	1.9*	—	—	3.8	0.7*	1.2*
		°F	13	—	13	31	31	31
		FI	4.5	—	1.8	5.05	1.7	2.5
2.5 gm. every three hours	7	CM	.384	.147	.055	.439	.147	.055
		CT	.304	.097	.025	.481	.308	.115
		t	0.3*	0.3*	0.5*	—	—	—
		°F	12	12	12	—	—	—
		FI	1.2	1.5	2.2	—	—	—
3 gm. every three hours	7	CM	1.540	.585	.446	1.540	585	.446
		CT	.753	.441	.111	.481	.308	.115
		t	1.5*	0.4*	1.5*	3.6	0.8*	2.1
		°F	12	12	12	31	31	31
		FI	2.0	1.3	4.0	3.2	1.9	3.8

CM = mean level for caronamide.
CT = mean level for control.
t = t value for the difference between means.
* = t value not statistically significant.
°F = degrees of freedom.
FI = fold increase = $\frac{\text{mean caronamide level}}{\text{mean control level}}$.

TABLE II

Caronamide Effect for Selected Oral Series 100,000 Units Penicillin Every Four Hours

Doses of Caronamide	Number of Cases		Versus Own Control				Versus Group Control			
			1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.
2 gm. every four hours	14	CM	1.451	.741	.350	.171	1.451	.741	.350	.171
		CT	.118	.082	.042	.019	.304	.138	.102	.048
		t	2.3	2.1	2.1	2.0	3.5	3.8	2.8	2.3
		°F	26	26	26	26	71	71	71	71
		FI	12.3	9.0	8.3	9.0	4.8	5.4	3.4	3.6
3 gm. every four hours	17	CM	.811	.992	.674	.223	.811	.992	.674	.223
		CT	.468	.232	.150	.047	.304	.138	.102	.048
		t	1.1*	2.4	1.6*	1.5*	3.05	3.6	2.6	2.4
		°F	32	32	32	32	74	74	74	74
		FI	1.7	4.3	4.5	4.7	2.7	7.2	6.6	4.6
4 gm. every four hours	13	CM	1.900	1.634	.779	.394	1.900	1.634	.779	.394
		CT	.319	.142	.139	.089	.304	.138	.102	.048
		t	3.9	3.8	3.4	2.0	6.8	7.6	6.8	4.6
		°F	24	24	24	24	70	70	70	70
		FI	5.9	11.5	5.6	4.4	6.2	11.8	7.6	8.2
2 gm. every two hours	15	CM	1.266	.681	.565	.238	1.266	.681	.565	.238
		CT	.126	.104	.072	.040	.304	.138	.102	.048
		t	3.1	3.4	2.7	3.1	4.2	4.9	4.7	4.1
		°F	28	28	28	28	72	72	72	72
		FI	1.0	6.5	7.9	5.9	4.2	4.9	5.5	5.0

CM = mean level for caronamide.
CT = mean level for control.
t = t value for the difference between means.
* = t value not statistically significant.
°F = degrees of freedom.
FI = fold increase = $\frac{\text{mean caronamide level}}{\text{mean control level}}$.

control group. Whereas 8 per cent of those receiving caronamide did not maintain a level of .078 unit per c.c. for any of the hours, the incidence in the control group of those who did not maintain such a serum concentration was 26 per cent. These differences are highly significant when tested by the chi square method and indicate a definite advantage of the use of caronamide with penicillin over the use of penicillin alone.

TABLE III

Per cent of Patients Showing Caronamide Effect

		Number of Cases According to Hours	Per Cent of Patients with No Fold Increase at				Per Cent of Patients with No Fold Increase at				
			1st Hr.	2nd Hr.	3rd Hr.	4th Hr.	One of the Hours	Two of the Hours	Three of the Hours	Four of the Hours	Any of the Hours
Total series		1–106 2–106 3–102 4– 67	25	22	35	49	23	21	11	5	8
Total intramuscular series		1– 40 2– 40 3– 36 4– 6	35	30	50	50	25	30	8	17	10
Total oral series		1– 66 2– 66 3– 66 4– 61	18	17	27	49	21	17	14	3	6
		Number of Cases According to Hours	Per Cent of Patients without a Level of .078 or Higher at				Per Cent of Patients with a Level of .078 or Higher Continuously for					
			1st Hr.	2nd Hr.	3rd Hr.	4th Hr.	1 Hr.	2 Hrs.	3 Hrs.	4 Hrs.	All Hours	None of the Hours
Total series	CT	1–106 2–106	26	59	77	88	39	16	12	11	15	26
	CM	3–102 4– 67	8	16	36	52	8	25	28	44	49	8
Total intramuscular series	CT	1– 40 2– 40	8	58	78	33	50	25	14	33	23	8
	CM	3– 36 4– 6	10	27	53	50	18	32	36	50	48	10
Total oral series	CT	1– 66 2– 66	38	59	76	90	32	11	11	8	11	38
	CM	3– 66 4– 61	8	9	27	52	3	20	24	49	50	8

CT—control

CM—caronamide. All percentage figures have been rounded.

The figures for the selected oral and intramuscular series are essentially the same as those for the total oral and total intramuscular groups respectively, and are thus excluded from the table.

Evidence of acute toxicity to caronamide was not observed, save for 10 instances of nausea and/or vomiting. This complication in most instances, however, may be attributable to mechanical irritation of the gastrointestinal tract caused by the large 0.5 gm. caronamide tablets when doses of 3 to 4 gm. every three to four hours were employed. None of the 22 patients who received second courses of the drug had evidence of fever, rash,

or conjunctivitis. We have not studied chronic toxicity of caronamide in a sufficiently large group of patients to make any deductions. One patient, however, received 12 gm. per day for 56 days without ill effect.

Twelve patients in our series were over the age of sixty. These patients showed no difference in response to caronamide administration than did other patients who were younger than 60 years.

Other investigators [11] have noted that caronamide will prolong the concentrations of penicillin in the blood for from four to eight hours following administration of 100,000 units intramuscularly. We became interested in the possibility of maintaining the concentrations of penicillin in the blood following the administration of a large single dose of penicillin plus caronamide at regular intervals thereafter. Consequently, one million units of crystalline penicillin G was given intramuscularly to 12 patients in a single injection plus 4 gm. of caronamide which was continued at four hour intervals thereafter for 24 hours. Caronamide prolonged the concentrations of penicillin in the blood (beyond the twelfth hour) in only one patient (until the sixteenth hour).

Comment

Oral caronamide is definitely efficacious in raising serum concentrations of penicillin. Furthermore, its effect is independent of the route of administration of penicillin. Seeler and associates [11] and Strauss and coworkers [12] have reported similar experiences. Since concentrations of penicillin in the blood can usually be raised to desired levels with greater facility following parenteral rather than oral administrations, we believe that caronamide will be used to best clinical advantage in conjunction with oral penicillin. It is well established that serum concentration following oral administration shows tremendous variation due to differences in the ability of patients to absorb the antibiotic. Our results indicate that 2 to 4 gm. of caronamide when administered with 100,000 units of oral penicillin give adequate serum concentrations for three to four hours in the majority of patients, a great improvement over the use of penicillin alone. It should be borne in mind, nevertheless, that approximately 8 per cent of patients receiving caronamide show no effect (either by measurement of fold increase or by ability to maintain a level of .078 unit per c.c. of penicillin continuously for all of the hours) regardless of the route of administration of penicillin.

In general the recommended dose is 4 gm. given every four hours. Seeler and his associates [11] reported that in patients over the age of 60 the effect of caronamide can be obtained with one-half the dose employed in younger individuals. We noted no such differences in the 12 patients over the age of 60 in our series of 106 patients.

Others as well as we have not observed any acute or chronic toxic effect in patients other than nausea and vomiting. Crossen [13, 14] has commented that in view of the chemistry of the compound and extensive experience during the past 12 years with sulfonamides which are related chemically to

caronamide, widespread use of caronamide will undoubtedly reveal some type of sensitivity or toxic manifestations. A suspension of caronamide * has recently appeared which contains 3 gm. of the drug per tablespoon. This preparation should decrease the incidence of nausea and vomiting if, as we believe, they are caused from mechanical irritation of the gastrointestinal tract by the bulky caronamide tablets.

Since experience with the use of caronamide has been brief, many problems concerning the use of caronamide with penicillin remain for future investigation. We are reporting the results of our study on one phase of the problem, namely the effect of caronamide in increasing the height of the concentration of penicillin in the blood following intramuscular and oral administration. The questions of chronic toxicity and the optimal penicillin-caronamide dosage and time relationship are still unsettled. The effect of caronamide on the oral administration of penicillin is obvious. When penicillin is administered parenterally, it may be more economical to increase the dose of penicillin rather than give caronamide if higher and more sustained concentrations of penicillin are desired.

Summary and Conclusions

1. Caronamide was administered orally to 106 patients in an effort to determine its ability to increase the concentrations of penicillin in the serum.

2. Caronamide increased the height of the serum penicillin concentrations for at least one of the hourly intervals tested in 92 per cent of the patients.

3. The average increase in serum penicillin concentrations attained with the use of penicillin plus caronamide over that obtained with the use of penicillin alone was approximately fourfold, regardless of the route of administration of penicillin.

4. The acute toxicity of caronamide is negligible. The order of chronic toxicity is as yet undetermined.

5. A recommended dose of caronamide is 4 gm. given every four hours.

6. Caronamide is used to best advantage clinically in combination with oral penicillin.

BIBLIOGRAPHY

1. Sprague, J. M., Ziegler, C., Craegoe, E. J., and Miller, C. S.: 4′ carboxyphenylmethanesulfonanilide. To be published.
2. Beyer, K. H.: New concept of competitive inhibition of the renal tubular excretion of penicillin, Science, 1947, cv, 94.
3. Beyer, K. H., Russo, H. F., Patch, E. H., and Miller, A. K.: A new concept of competitive inhibition of penicillin, Am. Jr. Med. Sci., 1947, ccxiii, 246.
4. Rake, G., and Richardson, A. P.: Pharmacology of penicillin, Ann. New York Acad. Sci., 1946, xlviii, 143.
5. Beyer, K. H., Russo, H. F., Miller, A. K., Patch, E. A., and Verwey, W. F.: The inhibitory effect of caronamide on the renal elimination of penicillin, Am. Jr. Physiol., 1947, cxlix, 355.

* Cremostaticin.

6. Beyer, K. H., Russo, H. F., Patch, E. A., and Tillson, E. A.: Caronamide: Its pharmacological properties. To be published.
7. Beyer, K. H., McKinney, S. E., Tillson, E. A., and Green, C. W.: Caronamide: Its toxicologic effects. To be published.
8. Verwey, W. F., and Miller, A. K.: The effect of caronamide upon penicillin therapy of experimental pneumococcus and typhoid infections. To be published.
9. Rammelkamp, C. H.: A method for determining the concentration of penicillin in body fluids and exudates, Proc. Soc. Exper. Biol. and Med., 1942, li, 95.
10. Hill, B.: Principles of Medical Statistics, Third edition, 1945, The Lancet Limited, London.
11. Seeler, O. S., Wilcox, C., and Finland, M.: Enhancement of blood levels by caronamide during intramuscular administration of penicillin, Jr. Lab. and Clin. Med., 1947, xxxii, 807.
12. Strauss, E., Richberg, P. L., Saba, P. Z., and Alexander, J. E.: Enhancement of plasma penicillin concentrations by caronamide and sodium benzoate, Jr. Lab. and Clin. Med., 1947, xxxii, 818.
13. Shaw, C. C., Boger, W. P., Crossen, J. W., Kemp, W. W., Ling, W. S. M., and Duncan, G. G.: Enhancement of penicillin blood levels by means of a new compound, caronamide, Am. Jr. Med., 1947, iii, 206.
14. Crossen, J. W., Boger, W. P., Shaw, C. C., and Miller, A. K.: Caronamide and penicillin, Jr. Am. Med. Assoc., 1947, cxxxiv, 1528.

CASE REPORTS

HEMOLYTIC ANEMIA ASSOCIATED WITH ATYPICAL HEMAGGLUTININS *

By William J. Kuhns, M.D., *Salt Lake City, Utah,* and Philip F. Wagley,† M.D., *Boston, Massachusetts*

There are in the literature scattered reports of cases of hemolytic anemia with demonstrable atypical iso- and autohemagglutinins. Reisner and Kalkstein [1] in 1942 found in the literature 54 case histories of patients with anemia whose bloods showed autohemagglutination. They reported an additional case of hemolytic anemia with autohemagglutinins. Wiener,[2] Baar,[3] Kracke and Hoffman,[4] Evans,[5] and Rennert and McShane,[6] have reported cases of hemolytic anemia associated with autohemagglutinins active at 37° C.

Callender and Paykoc [7] recently studied the sera of 100 patients who had been transfused with a total of 958 pints of whole blood. Two patients with hemolytic anemia, one of whom had an associated lymphatic leukemia, showed autohemagglutination at 37° C., room temperature, and 4° C. The sera did not agglutinate any other than the patient's own cells at 37° C.

Boorman, et al.[8] observed the development of atypical isohemagglutinins active at 37° C. following transfusion of whole blood to three patients. Two other cases, following transfusions, developed atypical cold isohemagglutinins, and one other developed a cold autohemagglutinin.

This communication is concerned with observations made in a fatal case of hemolytic anemia characterized by the presence of a high concentration of a panhemagglutinin effective only at low temperatures (cold hemagglutinin) as well as a separate hemagglutinin active at body temperature against the patient's cells and 63 per cent of red blood cells of Groups O and A.

Materials and Methods

The patient's blood (type A_1 N Rh_1) was collected in a warm syringe and placed in serological tubes at room temperature until clot formation occurred. The specimens were then centrifuged and the supernatant serum drawn off and placed in the icebox until tested. More than the usual number of saline washings of the red cells were necessary, as they still tended to agglutinate following three such procedures. This tendency disappeared after a total of 12 saline washings. Therefore, the cells were washed 12 times in saline initially warmed to 37° C. and centrifuged in warmed centrifuge cups. Titrations for autohemagglutinins were done by mixing a 2 per cent saline suspension of the patient's own cells with equal aliquots of serial dilutions of the patient's serum.

* Received for publication June 15, 1948.
From the Department of Medicine, School of Medicine, The Johns Hopkins University and the Baltimore Rh Typing Laboratory, Baltimore, Maryland.
† Research Fellow of the American College of Physicians.

Titrations for isohemagglutination were determined by utilizing 2 per cent saline suspensions of A_1 Rh_1 erythrocytes (washed three times at room temperature with physiological saline) in equal portions of serial dilutions of the patient's serum. The serum was titered serially for auto- and isohemagglutination at 8° C. and 37° C. shortly after withdrawal from the patient. All tubes were incubated at the desired temperature for one hour. The titrations for cold agglutinins were then placed in the refrigerator for an additional 12 to 18 hour period.

The experimental criteria of Stats and Wasserman [9] for cold hemagglutination were carried out. These included (a) agglutination of homologous erythrocytes at low temperature with reversal of the reaction upon increasing the temperature, (b) agglutination of the resuspended cell serum mixture upon chilling, (c) exhaustion of the agglutinins in the serum by absorption with erythrocytes at low temperature, (d) release of the agglutinins from the cold agglutinated erythrocytes by raising the temperature to approximately 37° C. Hemagglutinin titers in table 1 are expressed in units, each unit being the reciprocal of the dilution factor.

Specificity of the patient's warm agglutinating antibodies was determined by the use of a series of 2 per cent saline suspensions of washed erythrocytes which had been typed for A, O, M, N and Rh and its subtypes by the use of the corresponding antisera. Equal portions of the cells and serum suspensions were incubated for one hour at 37° C., centrifuged at moderate speed and read microscopically (table 2).

Isolation of the cold hemagglutinin (panagglutinin) from the warm hemagglutinin was accomplished by the following adsorption technics: saline suspensions of homologous type red blood cells which, on previous testing, had shown no agglutination at 37° C. with this serum were centrifuged and the supernatant saline withdrawn. Equal portions of the packed red cells and the patient's serum were placed in serological tubes and incubated with intermittent agitation at 8° C. and at 37° C. for a period of two hours. (Table 3). The 37° C. serum cell suspension was centrifuged in warmed cups and the supernatant withdrawn (Sample A). The 8° C. serum cell suspension was then centrifuged in ice-filled cups and the serum removed (Sample B). The supernatant serums from both aliquots were then titered for cold hemagglutinins, and also the supernatant serum from the 8° C. aliquot (Sample C) was titered for warm hemagglutinins. Saline suspensions of homologous type cells which agglutinated in the patient's serum at 37° C. were similarly treated, the supernatants from 37° C. aliquots being tested for warm and cold hemagglutinins (Samples D and E).

The in vitro transference of the patient's antibodies from her own cells to other normal cells was demonstrated by a method similar to one described elsewhere.[10] The patient's washed cells were suspended in three times their volume of normal saline and kept in a water bath at 56° C. for eight minutes with gentle agitation. The suspension was then centrifuged in cups heated to 56° C. and the supernatant was removed. Each eluate was divided into three portions. To each was added an equal portion of a washed suspension of normal group O cells. The three suspensions were kept for 12 hours at 8°, 24°, and 37° with intermittent agitation. Following this, the cells were washed with warm saline and suspended in 30 per cent bovine serum albumin. Readings were made after a two hour period of incubation.

The Ham, Donath-Landsteiner, serum bilirubin and osmotic fragility tests were performed according to standard technics.[11, 12, 13, 14] The effect of carbon dioxide was studied according to a previously described method.[15]

Case Report

L. M. was a 43 year old colored housewife admitted in a comatose state via the Johns Hopkins Hospital accident room to the gynecological service. Relatives stated that the patient's *chief complaint* had been vaginal bleeding. A more adequate history obtained later showed the *family* and *past histories* to be non-contributory. The present illness began approximately 10 days prior to admission with intermittent vaginal bleeding. The degree of bleeding could not be obtained from the history. The patient denied hemoptysis, hematemesis, epistaxis, melena, hematuria or jaundice. She had no joint or abdominal pains, or leg ulcers. An adequate dietary history was unobtainable. There had been no apparent exposure to any unusual chemicals or drugs. The patient became extremely weak several days prior to her admission and, approximately 36 hours prior to being seen at the hospital, had been lethargic and relatively unresponsive. She was brought to the hospital and admitted to the gynecological service. *Physical examination* showed a temperature of 100°, a pulse rate of 122, a respiratory rate of 16, a systolic blood pressure of 130 and diastolic pressure of 60 mm. of mercury. The skin showed evidence of recent weight loss. No edema or petechiae were present. There were three superficial excoriated ulcers approximately 1.5 cm. in diameter on the knuckle of the right first finger, one on the right buttocks, and one on the inner aspect of the right thigh. The mucous membranes showed marked pallor. There was no glandular enlargement. The pupils were dilated and the eyes fixed. The media were clear and the optic discs and vessels were normal. In both fundi were round and flame-shaped hemorrhages with occasional Roth spots. There was no sinus or mastoid tenderness. The nasal septum was intact. The patient was partially edentulous and the few remaining teeth were carious. The tongue showed normal markings. The pharynx was not injected. The neck was supple. The trachea was in the midline and there was no tracheal tug. The cervical vessels were not distended. The breasts were pendulous and atrophic. Both lungs were clear to percussion and auscultation. There was no sternal tenderness. The precordial dullness was not increased. Heart sounds were of normal quality, and the rate was rapid. There was a presystolic gallop rhythm at the mitral area and the apex. No significant murmurs were heard. There was no abdominal tenderness or palpable organs or masses. There was no costo-vertebral angle tenderness. Pelvic examination revealed no discharge or unusual bleeding. The cervix was lacerated and the uterus felt slightly enlarged. No adnexae were palpable. The mucosa of the cervix and vagina showed a few small (1 to 3 cm.) whitish patches. The rectal examination revealed nothing unusual. The appendages showed no lesions other than those already described. The neurological examination was negative. The *laboratory* data showed a negative serological test for syphilis. There was a red cell count of 550,000 per cu. mm. Hemoglobin was 1.8 grams per 100 c.c. There were 22,000 leukocytes per cu. mm. The urine showed no abnormalities. The icterus index was 10. The differential count showed 6 per cent metamyelocytes, 82 per cent polymorphonuclear neutrophiles, 10 per cent lymphocytes, 2 per cent monocytes and numerous normoblasts. Vaginal cultures and blood cultures were negative.

Within the first 12 hours of the patient's stay in the hospital, 2,000 c.c. of group O blood were transfused with no apparent untoward clinical reaction. She regained consciousness and was apparently as rational as usual. Further laboratory studies performed several days after admission showed a serum non-protein nitrogen of 33 mg. per 100 c.c. Reticulocytes were 2.6 per cent. The red cell count was 2.08 million per

cu. mm. and the hemoglobin 6.2 grams per 100 c.c. The hematocrit was 20 per cent. The mean corpuscular volume was 96 cubic microns. The mean corpuscular hemoglobin concentration was 31 per cent. There were 6,350 leukocytes per cu. mm. There appeared to be slight increase in the platelets. The icterus index was 12. There was moderate anisocytosis and slight poikilocytosis. The osmotic fragility was normal. Warm auto- and isohemagglutinins were not demonstrable in the patient's serum on the second day after admission nor were there cold hemagglutinins present in

FIG. 1*a*. Thrombi in pulmonary vessels at various stages of formation and organization.

significant titer (table 1). The patient was thought to have marked anemia as a sequel to severe vaginal bleeding. The cause of the blood loss was not definitely ascertained. The patient was discharged on the eleventh hospital day.

She was seen in the dispensary one month after the beginning of her illness. At that time her hemoglobin was 6.2 grams per 100 c.c. The erythrocytes could not be counted because of marked autohemagglutination. The osmotic fragility was again

normal. The icterus index was 13. Four nucleated red cells were seen per 100 leukocytes. The patient was asymptomatic. However, she was admitted to the medical service one week later because of rapidly progressing weakness and "nervousness." There was no history of blood loss. Again the patient showed marked pallor. With the exception of her mental status there was only one essential change in physical examination from the time of her first admission, i.e., slight jaundice was

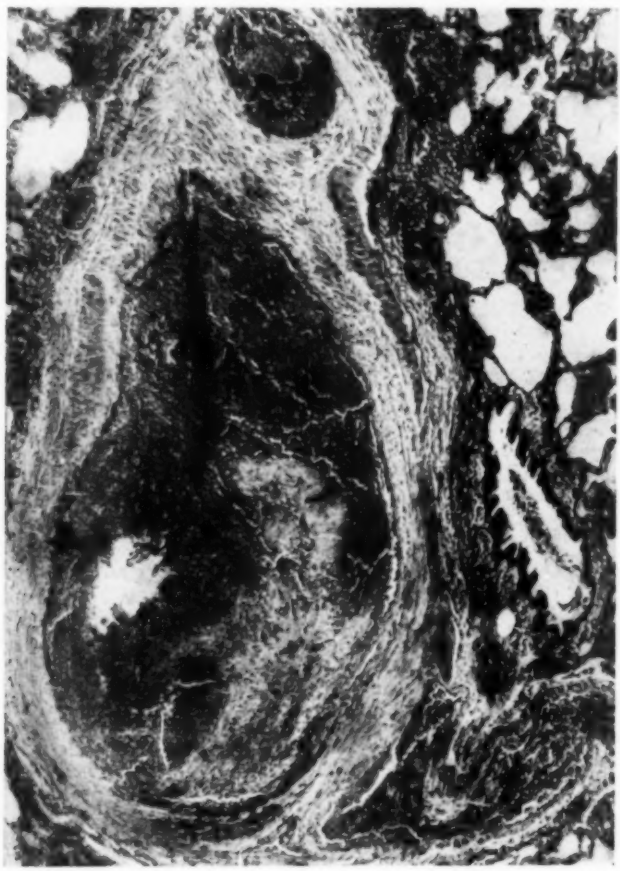


FIG. 1*b*.

noted. Laboratory data showed a high titer of autohemagglutinins at icebox temperature. The hemoglobin had fallen to 2.9 grams per 100 c.c. and the hematocrit was 9 per cent. The reticulocyte count was 21 per cent. There were 13,850 leukocytes per cu. mm. The icterus index was 23. No unusual leukocytes were noted on the blood smear. There were 6 nucleated red cells per 100 leukocytes. Sickling

preparations were negative. The urine showed a specific gravity of 1.016 and contained a trace of albumin. Urobilinogen in the urine was detectable in a dilution of 1 to 160. Otherwise the urine was normal. Prothrombin time was 23 seconds (greater than 50 per cent of normal). Serum non-protein nitrogen was 28 mg. per 100 c.c. Total serum protein was 7.69 grams per 100 c.c. Total serum bilirubin was 3.9 mg. per 100 c.c. with 0.9 mg. of the direct reacting type. Blood cholesterol was

FIG. 1*c*.

200 mg. per 100 c.c. Serum calcium was 9.9 mg. per 100 c.c., phosphorus 3.3 mg. per 100 c.c., and the alkaline phosphatase activity 2.5 units. The bromsulfonephthalein test showed 28 per cent retention at the end of 30 minutes (normal 0 to 5 per cent retention). Thymol turbidity was 11.4 units (normal 0 to 6 units) and the cephalin flocculation test was two plus. Roentgen-rays of the bones showed no lesions.

Sternal puncture showed only an increased percentage of normoblasts. Donath-Landsteiner and Ham tests were negative. No hemolytic activity of the serum was demonstrable with carbon dioxide by a technic described elsewhere.[15] A night specimen of urine was negative for hemoglobin by spectroscopic examination and negative for hemosiderin.[16] Cold hemagglutinins were present in a titer of 3,072 units. A bladder culture and a blood culture were both negative.

The patient responded well to numerous transfusions and experienced no apparent clinical transfusion reactions. Her cold hemagglutinin titer remained over 2,048 units. As repeated blood transfusions were necessary to maintain a satisfactory hemoglobin level, a splenectomy was considered advisable. The spleen, removed two and one half-months after the beginning of her illness, weighed 350 grams. Microscopically there were numerous large malpighian bodies. There was no dilatation of the sinuses or engorgement of the pulp. There were numerous mononuclear cells in the perilymphatic tissues. Thirty-three days following splenectomy the cold hemagglutinin titer was 96 units but for the first time a warm autohemagglutinin in a titer of 4 units was demonstrable.

In the five weeks that followed splenectomy, it was found that the patient still required transfusions and in this period she received a total of 10 liters of blood without apparent clinical reaction. The hemoglobin attained a level of 9 grams and remained there for four weeks at which time she was discharged apparently improved. At the time of discharge a moderate glandular enlargement was noted and the liver was enlarged three fingers'-breadth below the costal margin. The reticulocyte count was 16 per cent. The total bilirubin was 2.3 mg. per 100 c.c. with 1.1 mg. of the direct reacting type. Thymol turbidity was 11.8 units and the cephalin flocculation test was two plus. A test for heterophile antibodies was negative.

One month following the second discharge, the patient was seen in the dispensary acutely and critically ill. She had suddenly become quite weak and prostrate 24 hours previously. This was associated with extreme dyspnea. The physical examination showed a temperature of 102.4°, pulse rate of 136, respiratory rate of 52, systolic blood pressure 150 and diastolic 70 mm. of mercury. The patient was critically ill and the degree of dyspnea was out of proportion to her other symptoms. She was perspiring freely. There were marked pallor and slight icterus. Otherwise the examination showed no essential changes. The hemoglobin was 3 grams per 100 c.c. and the hematocrit was 17.6 per cent. The reticulocyte count was 50 per cent. Icterus index was 80. Leukocytes were 35,000 per cu. mm. On differential count there were 70 per cent polymorphonuclear neutrophiles, 23 per cent lymphocytes, and 7 per cent monocytes. There were 105 normoblasts per 100 leukocytes. There was marked aniso- and macrocytosis. Autohemagglutination was so great that it was grossly visible in the syringe used for venipuncture. The patient was given 1,500 c.c. of homologous type blood warmed at 37.5° C. This was done because of the high titer of cold hemagglutinin previously observed.

The tachycardia, tachypnea, and dyspnea continued. A friction rub became audible over the left posterior chest 24 hours after admission. On the second hospital day respirations suddenly ceased. Serum obtained from the patient on the last admission and before transfusions showed a cold hemagglutinin titer of 4,096 units, and a warm autohemagglutinin titer of 64 units. The clinical impression was severe hemolytic anemia associated with extensive intravascular agglutination and thromboses.

Autopsy (performed by Dr. Morgan Berthrong): The body at autopsy showed evidence of recent weight loss. The skin was clear. The sclerae were icteric. Moderate generalized glandular enlargement was noted. The peritoneal cavity contained 100 c.c. of cloudy yellow fluid; the peritoneal surfaces were smooth and glistening and showed no evidence of inflammation. In the thoracic cavity were fresh soft fibrous adhesions over the lower lobes of both lungs, particularly over the diaphragmatic surfaces.

The heart was not enlarged. Both epicardium and endocardium were smooth. The valves were delicate. The myocardium was homogeneous and of good color. On the pleura of the left lung were numerous lymphoid follicles and a few patches of fibrous roughening over its upper lobe. On section there was an amazing prominence of pulmonary vessels all of which contained red clots. The vessels at the periphery of the lung were dilated in the posterior and anterior portions. Posterior portions of the lower lobe contained a gelatinous edema coagulum. On the right there was a red clot in the main pulmonary artery. On section the right lung duplicated the left in appearance.

The liver was enlarged, weighing 2,100 grams, and showed distinct rusty pigmentation. The gall-bladder appeared normal but contained two pigmented stones. The pancreas on section contained prominent vessels filled with red clots. The kidneys were firm and the capsule adhered somewhat to the kidney surfaces. Kidney architecture was normal on section but definite rusty pigmentation of the renal parenchyma was seen; this was deeper in the cortex than in the pyramids. The cervix was lacerated and the vagina was roughened by hemorrhagic material. The uterus showed dilated vessels filled with clots. The uterine muscle was homogeneous. No joint or bone marrow abnormalities were noted grossly.

On microscopic section the lungs presented a striking appearance (see photographs). The vessels were extremely prominent and were plugged by numerous thrombi, both fresh and organizing. The capillaries of the alveolar walls were markedly distended by thrombi. The alveoli contained small amounts of protein precipitate. Microscopic sections of the liver showed a central necrosis of the hepatic tissue. Thrombi were also present in the smaller vessels of other organs, particularly the pancreas. Bone marrow sections showed marked hyperplasia of the erythrocytic series.

Experiments and Observations

As shown in table 1 there was a rising titer of cold and warm autohemagglutinins during the patient's clinical course. The first three serum studies showed no warm iso- or autohemagglutinins, although the cold hemagglutinin titer became quite high. Thirty-three days after splenectomy, and after numerous transfusions of type O and A Rh positive blood, examination of a fourth serum specimen demonstrated a decrease in cold autohemagglutinin titer. However, for the first time a warm autohemagglutinin in low titer was demonstrable. Furthermore, a warm isohemagglutinin effective against one of 24 bloods (type A_1 Rh_2 MN) was demonstrable in a titer of two units. Three months after splenec-

Table I

Titers of Cold and Warm Hemagglutinins at Various Times during the Clinical Course

Agglutinins Active at	Titers for Cold and Warm Autohemagglutinins Patient's Serum Against a 2% Saline Suspension of Her Own Cells (Titer Readings Designate Units)				
	Dates on Which Specimens Were Collected				
	12/31/46	2/3/47	2/12/47	3/25/47*	5/19/47
8° C	16	3072	2048	96	4096
37° C	0	0	0	4	64

* Thirty-three days postsplenectomy.

tomy, the patient's warm auto- and isohemagglutinin titer had risen to 64 units and the cold hemagglutinin titer was 4,096 units.

The separability of the cold and warm hemagglutinins (on the sample obtained at the last admission before transfusions) was demonstrated as follows: (1) When tested against a panel of bloods the cold hemagglutinin showed no specificity for red cells (it was a panhemagglutinin) but the warm hemagglutinin showed definite specificity (table 2). Table 2 illustrates that the agglutinative pattern of the atypical warm isohemagglutinin in the patient's serum, when tested against a panel of bloods, was not predictable on the basis of the A (A_1 and A_2), O, M, N, Rh, or Hr blood types. By testing her serum with various combinations of A and O red cells which had been further subtyped with M, N, Rh, Rh′, and Rh″ sera, it was found that 63 per cent of 156 different bloods were agglutinated. (2) Cells not agglutinable at 37° C. were reversibly agglutinable at icebox temperature. Adsorption experiments with agglutinable and non-agglutinable (at 37° C.) homologous red blood cells were then performed, as described under "Materials and Methods."

TABLE II

Presentation of Data on Agglutinogens Studied. There was no apparent relationship between the agglutinating activity of the patient's serum and the agglutinogens recorded.

Type of Cell	Reaction of Patient's Serum (blood type A_1 N Rh_1) with Various Red Blood Cell Types at 37° C. (sample of 5/19/47)	
	Reaction with Serum of Patient	
	Positive	Negative
O	42	31
A_1	36	7
A_2	8	4
M	10	2
N	17	8
Rh_1	23	8
Rh_2	5	1
Rh_0	2	3
Rh″	1	0
Rh negative (Hr positive)	15	5
Total	149	69

Separation of the warm from the cold hemagglutinin was possible by means of adsorption technics (table 3). When cells showing no agglutination at 37° C. were incubated with the patient's serum at 37° C., titration of the supernatant (Sample A) at 8° C. demonstrated the presence of cold hemagglutinins. When adsorption was carried out at 8° C., titration of the supernatant (Sample B) at 8° C. showed no agglutination, i.e., the cold hemagglutinin had been adsorbed. However, when the supernatant (Sample C) was titered at 37° C. with cells previously known to have been agglutinated by the serum at 37° C. warm agglutinins were still demonstrable. Hence, the cold hemagglutinin was adsorbed but the warm hemagglutinin remained intact. When agglutinable (at 37° C.) A_1 Rh_1 red cells were incubated with the patient's serum at 37° C. for two hours with intermittent agitation and the supernatant removed after centrifugation, the serum (Sample D) no longer reacted with cells previously agglutinated at 37° C., i.e., the warm hemagglutinin had been adsorbed. However, the same aliquot (Sample E) was still positive in considerable titer against both agglutinable cells

and non-agglutinable cells (at 37° C.) when the titrations were incubated at 8° C. When this adsorbed serum was set up qualitatively against a panel of 10 bloods (typed for A_1, A_2, O, M, N, Rh and subtypes) both at 8° and 37° C., agglutination occurred with all bloods incubated at 8° C. but with none of the bloods incubated at 37° C. Thus it was possible to adsorb the warm hemagglutinin from the patient's serum but at the same time leave the cold hemagglutinin intact.

TABLE III

Presentation of Data Showing Separability of Cold and Warm Hemagglutinins

Summary of Adsorption Experiments Using Patient's Serum and Appropriate Cells

Thermal Reactivity of Cells Employed for Adsorption	Patient's Adsorbed Serum		Reaction of Test Cell with Adsorbed Serum
	Temperature at Which Adsorption Was Done	Adsorbed Supernatant Titered for	
Agglutination at 8° C. No agglutination at 37° C.	A. 37° C.	cold hemagglutinins	4 plus
	B. 8° C.	cold hemagglutinins	negative
	C. 8° C.	warm hemagglutinins	4 plus
Agglutination at 8° C. and 37° C.	D. 37° C.	warm hemagglutinins	negative
	E. 37° C.	cold hemagglutinins	4 plus

Elution experiments (described under "Materials and Methods") demonstrated that it was possible passively to transfer the hemagglutinins to normal red blood cells. Following sensitization of normal red cells with the eluate from the patient's heated cells, the addition of 30 per cent bovine serum albumin resulted in agglutination of the cells at 8°, 24° and 37° C.

DISCUSSION

There are two aspects of the clinico-pathological picture exhibited by this patient which are worthy of detailed consideration. The first is a consideration of the possible rôle of autohemagglutination and thrombosis in the etiology of the hemolytic anemia and the second is a consideration of the immunological aspects of the agglutinins found in this patient.

The association of agglutination of red blood cells with resulting increased fragility has been previously demonstrated.[18] Hemoglobinemia and hemoglobinuria have been produced in two patients with high titers of cold hemagglutinins by exposure of a limb to cold.[19, 20] Such observations as well as the hemolytic anemias of atypical pneumonia [21] have suggested to others [22] that the "cohesion of erythrocytes may lead to their prompt mechanical destruction while in motion in the circulation." Thus intravascular agglutination may conceivably have resulted in hemolysis in this case.

Ham and Castle [23, 24, 25] have repeatedly suggested other mechanisms associated with red blood cell agglutination that would contribute toward or acutely cause hemolysis. As has been indicated in this case and suggested by other clinical observation,[26] intravascular erythrostasis occurred in small vessels. In vivo experiments by Emerson et al.[27] have demonstrated that intrasplenic stasis may

be associated with localized hemoconcentration and followed by increased hypotonic fragility of red blood cells. Concanavallin A, in low concentration, causes agglutination but not a significant degree of hemolysis or alteration in hypotonic fragility of red blood cells under certain specified in vitro conditions.[28] However, the injection of this material into dogs and rabbits causes agglutination of red blood cells associated with a rapid drop in hematocrit suggesting a trapping and concentration of cells in small vessels of the body. Following such injections cells appearing in the periphery show increased hypotonic fragility. The appearance of these cells is associated with hemolytic anemias of various degrees, sometimes fatal. It has been suggested that the mechanism of erythrostasis and localized hemoconcentration are comparable in their effects to the effects of sterile in vitro incubation.[24, 27] Following the latter procedure red blood cells show spherocytic tendencies, increased hypotonic fragility and increased cell volume. These investigators have carried their reasoning one step further and suggested that increased degrees of erythrostasis that occur in the spleen may cause increased destruction of blood in congenital hemolytic icterus, icterus neonatorum, acute hemolytic anemias associated with sulfonamides, etc.[24, 27] Certainly if an increased degree of erythrostasis is of importance in blood destruction the degree of stasis occurring in this case should play a primary rôle in the hemolytic anemia observed.

The autohemagglutination observed in the present case was marked. As the patient's condition progressed, the presence of a hemagglutinin active even at 37° C. became evident in relatively high titers. That such hemagglutinins were active in vivo was suggested by several observations. Venipuncture of the patient was attended by gross clumping of her erythrocytes in the warm syringe. In the latter part of her illness warming the syringe to body temperature prior to venipuncture did not lessen this clumping tendency. The second observation which suggested in vivo agglutination and even multiple thromboses was the extreme dyspnea and tachypnea of the patient. This was strikingly out of proportion to her physical signs. Soon after admission the patient developed a pleural friction rub. This clinical picture suggested the possibility of multiple pulmonary thromboses.

This clinical impression was verified at autopsy, where the lungs presented a striking appearance. The vessels were extremely prominent and were plugged by numerous thrombi. Microscopically the degree of thrombosis was even more impressive (see photographs). The capillaries of the alveolar walls were markedly distended by thrombi and under low power resembled a heavy wire mesh. The remainder of the histological structure of the alveolar walls was obliterated by the distended capillaries. The alveoli contained a small amount of protein precipitate which suggested some pulmonary edema. It seems logical to assume that the autohemagglutination accounted for the extensive multiple thromboses. If in vivo autohemagglutination leads to hemolysis, then these observations would indicate adequate cause for the fatal hemolytic crisis of this patient.

The observations of Granick [29] on horse spleen bear on the Castle-Ham concept. By the production of a black insoluble iron sulfide Granick studied the distribution of inorganic iron. Examination of freshly teased horse spleen revealed spherocytes and large red blood cells containing diffuse inorganic iron.[29] This observation was interpreted as indicating intraerythrocytic disintegration of the heme molecule in the spleen. As normal horse blood may contain amounts

of ferrihemoglobin in the order of 20 per cent of the total hemoglobin present [30] it was suggested by Granick that the spleen of the horse may have oxidative effects on erythrocytes stagnant in its sinuses resulting in their eventual lysis.

The second aspect of this case worthy of study pertains to the immunological characteristics of the patient's serum.

"Polyagglutinability" is a term applied by some [31] to changes in agglutinability of erythrocytes following in vitro contamination with bacteria. Such exposure of cells may render them agglutinable to normal serum. This has been termed the "Heubner-Thomsen-Freidenreich phenomenon." Levine and Katzin [32] have described observations which suggest that a somewhat similar phenomenon may occur in vivo. They reported the case of a four-year-old child who had measles complicated by bronchopneumonia, and empyema due to a pneumococcus Type I. Although the patient had group O red blood cells, 15 per cent of various serums, irrespective of blood group, agglutinated them. However, no unusual agglutinin was described in the patient's serum. The effective agglutinin present in 15 per cent of the population was adsorbable by the patient's cells. Four months after the illness the cells of the patient no longer possessed this ability. Sachs and Gaffney [31] reported two cases in which the red cells showed polyagglutinability. The cells (group O) of one patient were agglutinated by 89 per cent of normal serums in dilutions of 1 to 16 and 1 to 32 at room temperature and refrigerator temperature respectively. The changes observed in the present patient differ from the above characteristics of polyagglutinability. In the first place, the serums of the above mentioned patients did not contain the effective agglutinin. Furthermore, the phenomenon of polyagglutinability does not occur at 37° C., but only at lower temperatures (25° C. or below).

Neter [33] has reported a 26 year old male patient with a *Streptococcus viridans* endocarditis who, after three whole blood transfusions, developed an irregular isohemagglutinin which was effective against 20 per cent of group O red blood cells at icebox temperature and at 37° C. The isohemagglutinin was present only in a titer of 1 to 2 and could not be demonstrated late in the disease process.

The occurrence of cold hemagglutinins in hemolytic anemias has been demonstrated by Boorman,[8] Finland,[34] McSweeney,[35] and Siebens.[36] It has been suggested by Wiener,[2] Baar,[3] Reisner and Kalkstein,[1] and Young [37] that the warm hemagglutinins developing in some cases of hemolytic anemias were cold hemagglutinins which attained a thermal amplitude of 37° C. In the present case, it appears from the available data that at least two separate atypical serological components were present: (1) a non-specific panhemagglutinin which reacted only at icebox temperature and (2) a hemagglutinin which reacted with the patient's cells and 63 per cent of red cell samples from group A and O bloods; whether the capacity to agglutinate the patient's own, in addition to other red blood cells, represents the action of more than the described components is not known. These atypical hemagglutinins occurred in addition to the naturally occurring anti-B hemagglutinin which was present in a demonstrable titer of 64 units. The separability of the two atypical hemagglutinins was suggested first by the difference in time of appearance and second by the independence in fluctuation in concentration. When the warm hemagglutinin titer was first demonstrable the cold hemagglutinin titer was much lower than it had been on previous occasions. Subsequently the warm hemagglutinin titer rose to higher

levels while the cold hemagglutinin titer did not rise much above the previous point it attained (at which time no warm hemagglutinin titer was demonstrable). The presence of qualitative differences was established by the following facts. A hemagglutinin reacting with and adsorbed by the patient's own cells at 37° C. also agglutinated 63 per cent of normal red cells from 156 group A and O blood samples at 37° C. A panhemagglutinin active only in the cold (cold hemagglutinin) was also present. Adsorption experiments proved the separability of the atypical warm cell-specific hemagglutinin from the non-specific cold hemagglutinin. Since the warm hemagglutinin was not adsorbed non-specifically by red cells that were unagglutinated (at 37° C.) by the serum, and the warm hemagglutinin was independent of known blood groups, it is possible that it was specific for an unknown agglutinogen contained in certain of the normal red cells and those of the patient.

Young [38] has pointed out that patients of blood groups A and AB may develop increased alpha$_1$ or alpha$_2$ isohemagglutinin titers following transfusions of the heterologous type A blood and thus develop a possible hemolytic reaction on this account. That such isohemagglutinins cannot account for the observations made in this patient is apparent from study of table 2. The serum of the patient gave both positive and negative reactions with a series of A_1 and A_2 bloods in which the possible effects of other known blood group antigens were excluded with a few rare exceptions which are noted below.

Wiener [39, 40] observed the development of anti-P hemagglutinins in two post-transfusion serums. Anti-P serum was not available for the study of this case. However, the ratio of positive to negative reactions did not concur with the ratios obtained by Dahr [41] in his study of P positive and P negative individuals. Furthermore, anti-P agglutinins are usually quite weak and react most distinctly at low temperatures. That the present warm agglutinin is identical with the anti-X of Andresen [42] would seem highly unlikely on purely a statistical basis. As was pointed out originally, 94 per cent of human erythrocytes contain X agglutinogen. Only 63 per cent of the panel of bloods reacted to the warm hemagglutinin present in this case.

Callender et al.[43] have observed the development of warm atypical isohemagglutinins following multiple transfusions. In an anemia patient who had received repeated transfusions, they were able to identify four isohemagglutinins. One hemagglutinin, designated after the donor's name as anti-Lutheran, agglutinated 8 to 9 per cent of several hundred bloods regardless of A, B, O, M, N, P, or Rh types. They demonstrated that the Lutheran agglutinogen was inherited as a Mendelian dominant. Three other antibodies subsequently appeared in the patient's serum following further transfusions; anti-St, anti-Willis, and anti-Levay. Willis antigen was found in 7 per cent of the British population as a Mendelian dominant inherited in a manner relating to Rh but not to A, B, O, M, N, or P. The Levay antigen was found only in the blood of one of the donors and his father. Several hundred bloods examined at random did not show this hemagglutinogen.

Summary

1. The present case is that of a patient who developed during observation two atypical hemagglutinins in high titer associated with multiple transfusions.

2. A non-specific panhemagglutinin was observed (cold hemagglutinin) which reacted with, and was adsorbed by, all types of cells tested including those of the patient at low temperature.

3. A warm hemagglutinin was demonstrated which reacted at 37° C. with the patient's cells and those of 63 per cent of bloods compatible for A_1, A_2, O, M, N, Rr, and Hr. It could be adsorbed only by those cells agglutinated by it at 37° C. This hemagglutinin was possibly specific for an unidentified agglutinogen, one apparently present in the patient's own cells.

4. The patient developed a severe hemolytic anemia, characterized by hyperbilirubinemia, reticulocytosis, nucleated red cells, and generalized intravascular thrombosis. It is suggested that the autohemagglutination contributed to the intravascular thromboses and that both factors may have produced erythrostasis with further increase in blood destruction.

Acknowledgment: The authors wish to thank Dr. M. S. Sacks for his suggestions and Dr. Morgan Berthrong for his assistance.

BIBLIOGRAPHY

1. Reisner, E. H., and Kalkstein, M.: Auto hemolysinic anemia with auto agglutination: improvement after splenectomy, Am. Jr. Med. Sci., 1942, cciii, 313–322.
2. Wiener, A. S.: Hemolytic transfusion reactions. 1. Diagnosis with special reference to the method of differential agglutination, Am. Jr. Clin. Path., 1942, xii, 189–199.
3. Baar, H. S.: Normal life of the red cell, Lancet, 1945, ii, 724.
4. Kracke, R., and Hoffman, B.: Chronic hemolytic anemia with auto agglutination and hyperglobulinemia: report of a fatal case, Ann. Int. Med., 1943, xix, 673.
5. Evans, R. S.: Acute hemolytic anemia with auto-agglutination, Stanford Med. Bull., 1943, i, 178.
6. Rennert, W., and McShane, J.: The role of autohemagglutinins in hemolytic anemias, South Med. Jr., 1947, xl, 973–980.
7. Callender, S. T., and Paykoc, Z. V.: Irregular hemagglutinins after transfusion, Brit. Med. Jr., 1946, i, 119–121.
8. Boorman, K. E., Dodd, B. E., Loutit, J. F., and Mollison, P.: Results of transfusion of blood to recipients with cold agglutinins, Brit. Med. Jr., 1946, i, 751–754.
9. Stats, D., and Wasserman, L. F.: Cold hemagglutination: an interpretive review, Medicine, 1943, xxii, 363–424.
10. Evans, R. S., Duane, R. T., and Behrende, V.: Demonstration of antibodies in acquired hemolytic anemia with anti-globulin serum, Proc. Soc. Exper. Biol. and Med., 1947, lxiv, 372–375.
11. Ham, T. H., and Dingle, J. H.: Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria: certain immunological aspects of the hemolytic mechanism with special reference to serum complement, Jr. Clin. Invest., 1939, xviii, 657–672.
12. Mackenzie, G. M.: Paroxysmal hemoglobinuria. A review, Medicine, 1929, viii, 159–191.
13. Malloy, H. T., and Evelyn, K. A.: Determination of bilirubin with photoelectric colorimeter, Jr. Biol. Chem., 1937, cxix, 481–490.
14. Wintrobe, M. M.: Clinical hematology, 1942, Lea and Febiger, Philadelphia.
15. Wagley, P. F., Siebens, A. A., and Zinkham, W. H.: A note on studies of hemolysis in paroxysmal (cold) hemoglobinuria, Am. Jr. Med., 1947, ii, 342–346.
16. Ross, J. F.: Hemoglobinemia and hemoglobinuria, New England Jr. Med., 1945, ccxxxiii, 691–766.
17. Sacks, M. S., Kuhns, W. J., and Jahn, E.: The clinical significance of the Rh factor, South. Med. Jr., 1947, 47–53.

18. Stats, D.: Cold hemagglutination and cold hemolysis produced by shaking cold agglutinated erythrocytes, Jr. Clin. Invest., 1945, xxiv, 34–42.
19. Ham, T. H., Gardner, F. H., Wagley, P. F., and Shen, S. C.: Jr. Clin. Invest., 1948, xxvii, 538–539.
20. Hickey, M. D., and Malley, L. K.: Chronic hemolytic anemia with hemoglobinuria. In press.
21. Finland, M. Peterson, O. L., Allen, H. E., Samper, B. A., and Barnes, M. W.: Cold agglutinins: Cold isohemagglutinins in primary atypical pneumonia of unknown etiology with a note on occurrence of hemolytic anemia in these cases, Jr. Clin. Invest., 1945, xxiv, 458–473.
22. Shen, S. C., Castle, W. B., and Fleming, E. M.: Experimental and clinical observations on increased mechanical fragility of erythrocytes, Science, 1944, c, 387–389.
23. Ham, T. H., and Castle, W. B.: Studies on destruction of red blood cells. Relation of increased hypotonic fragility and of erythrostasis to the mechanism of hemolysis in certain anemias, Proc. Am. Philos. Soc., 1940, lxxxii, 411–419.
24. Ham, T. H., and Castle, W. B.: Mechanism of hemolysis in certain anemias: significance of increased hypotonic fragility and erythrostasis, Jr. Clin. Invest., 1940, xix, 788.
25. Ham, T. H., and Castle, W. B.: Relation of increased hypotonic fragility and of erythrostasis in certain anemias, Trans. Assoc. Am. Phys., 1940, lv, 127–132.
26. Stats, D., and Bullowa, J. O. M.: Cold hemagglutination with symmetrical gangrene of tips of the extremities, Arch. Int. Med., 1943, lxxii, 506–517.
27. Emerson, C. P., Jr., Shen, S. C., Ham, T. H., and Castle, W. B.: The mechanism of blood destruction in congenital hemolytic jaundice, Jr. Clin. Invest., 1947, xxvi, 1180.
28. Granick, S.: Non-hematin iron in erythrocytes, Proc. Soc. Exper. Biol. and Med., 1943, liii, 255–256.
29. Granick, S.: Iron and porphyrin metabolism in relation to the red blood cell, Ann. N. Y. Acad. Sci., 1947, xlviii, 657–681.
30. Ramsay, W. N. M.: Ferrihemoglobinemia (methemoglobinemia) in man and the horse, Biochem. Jr., 1944, xxxviii, 470–473.
31. Gaffney, J. C., and Sachs, H.: Polyagglutinability of red blood cells, Jr. Path. and Bact., 1943, lv, 489–492.
32. Levine, P., and Katzin, E. M.: Temporary agglutinability of red blood cells, Proc. Soc. Exper. Biol. and Med., 1938, xxxix, 167–169.
33. Neter, E.: Observations on abnormal isoantibodies following transfusions, Jr. Immunol., 1936, xxx, 255–259.
34. Finland, M., Peterson, O. L., Allen, H. E., Samper, B. A., and Barnes, M. W.: Cold agglutinins. 1. Occurrence of cold isohemagglutinins in various conditions, Jr. Clin. Invest., 1946, xxiv, 451–452.
35. McSweeney, J. E. J., Mermann, A. C., and Wagley, P. F.: Cold hemagglutinins in sickle cell anemia, Am. Jr. Med. Sci., 1947, ccxiv, 542–544.
36. Siebens, A. A., Zinkham, W. H., and Wagley, P. F.: Observations on the mechanism of hemolysis in (cold) hemoglobinuria, Blood, 1948, iii, 1367–1380.
37. Young, L. E., and Lawrence, J. S.: Atypical hemolytic anemia, Arch. Int. Med., 1946, lxxvii, 151–178.
38. Young, L. E.: Studies of the subgroups of blood groups A and AB. I. The active and passive acquisition of alpha$_2$ agglutinins by A_2 patients as a result of blood transfusion, Jr. Immunol., 1945, li, 101–116.
39. Wiener, A. S.: Hemolytic transfusion reactions. III. Prevention with special reference to the Rh and cross match tests, Am. Jr. Clin. Path., 1942, xii, 303–311.
40. Wiener, A. S., and Peters, H. R.: Hemolytic reactions following transfusions of blood of the homologous group, Ann. Int. Med., 1940, xiii, 2306–2322.

41. Dahr, P., and Zehner, M.: Die Bisherigen Erblichkeitsuntersuchungen über den Blutfaktor P und die Verwendung der P Bestimmung in Vaterschaftsprozessen, Deutsch. med. Wchnschr., 1941, lxvii, 71–72.
42. Andresen, P. H.: Nachweis eines Immunagglutinins und einer Dement aprechenden neuen Bluttgruppenesigenschaft, Ztschr. f. Immunitats., 1935, lxxxv, 226–232.
43. Callender, S., Race, R. R., and Paykoc, Z. V.: Hypersensitivity to transfused blood, Brit. Med. Jr., 1945, ii, 83–84.

OBSERVATIONS ON THE FATE OF THE ACCESSORY CONDUCTOR IN WOLFF-PARKINSON-WHITE SYNDROME: REPORT OF A CASE DEMONSTRATING RETURN TO NORMAL CONDUCTION FOLLOWING ACUTE ILLNESS *

By David Littmann, M.D.,† *West Roxbury, Massachusetts*

The electrocardiographic syndrome of Wolff, Parkinson and White [7] is commonly believed to result from the presence in the heart of an accessory atrioventricular conducting structure similar to the Bundle of Kent of some animals. This serves as a short-circuiting device around the normal A-V system and delivers the impulse prematurely to one ventricle, usually the right. The resulting electrocardiographic pattern is that of bundle branch block with a short P-R interval. The mechanism was first suggested by Holzman and Scherf [5] and by Wolferth and Wood [6]; it was duplicated experimentally by Butterworth [2] and demonstrated histologically by Wood, Wolferth and Geckler [8] in a child who during life exhibited this curious syndrome.

Although it has been noted in an infant of 14 weeks [1] (who also had coarctation of the aorta) and occasionally in subjects of middle age, this condition is most commonly encountered in young adult males. Most cases recently have been reported from the armed forces. In spite of isolated exceptions, one gets the impression from the literature that Wolff-Parkinson-White syndrome occurs largely in young adult males as the result of an anomaly which is present at birth. Additionally, it would appear that the electrocardiographic stigmata tend to disappear with advancing years. This is apparent from the almost total absence of the syndrome among the aged and is even more striking when one recalls that, by and large, the greatest number of electrocardiograms are made on older subjects. Contrariwise, the low incidence of this anomaly in the young may be partly explained by the fact that few tracings are ordinarily made on children. However, the incidence of one in 500 [3] to one in 400 [4] seen in young adults is not even remotely approached in juveniles.

We have, therefore, the curious phenomenon of an electrocardiographic syndrome in young adults which results from a congenital vestige but which is rarely

* Received for publication November 1, 1946.
Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.
† Chief, Cardiac Service, Veterans Administration Hospital, West Roxbury, Massachusetts.

manifest in childhood or in old age. One may, therefore, postulate that the accessory muscle bundle which is present at birth may not become operative until early adult life and then probably as the result of altered physiology of the heart and its conducting mechanisms. Such a change could come about from increased vagus activity or as the result of illness. Recent reports have stressed the comparatively high incidence of organic disease of the heart in association with Wolff-Parkinson-White syndrome. Subclinical rheumatic fever and equally obscure toxic myocarditis doubtless make this incidence even higher. It is suggested, therefore, that increasing vagus control or organic disease cause depression of the normal A-V conducting system, thus disturbing an existing equilibrium and permitting a dormant accessory pathway to assume an abnormal conducting function. If the aberrant pathway is coincidentally suppressed by the same disease no unusual conduction is expected. When the abnormal pathway retains its comparatively greater irritability and conductivity the syndrome of premature ventricular excitation becomes lasting.

Where the accessory atrioventricular channel has been functioning for some time and the syndrome of short P-R and long QRS is well established, changes in, or injury to, the conducting system may further alter the ventricular innervation. Such damage could be gradual as with progressive vascular depletion or more rapid as from acute ischemia or toxic illness. When the aberrant conductor has become sufficiently involved it recedes in activity and the normal A-V system resumes its function.

It would appear, therefore, that altered physiology of the normal conducting system or injury to it may permit an inactive vestigial pathway to assume an abnormal function of conduction and result in an electrocardiographic syndrome. Subsequently, toxic or degenerative states act to deprive the abnormal structure of that faculty and result in disappearance of the short P-R, long QRS pattern.

A case is presented which is, apparently, an instance of complete suppression of an aberrant atrioventricular conductor occurring during the course of and resulting from an acute illness.

Case Report

A 39 year old mail carrier was admitted to the hospital on April 5, 1946 complaining of fever, chills, weakness, substernal tightness, cough and bloody sputum. The illness began three weeks earlier with chilliness, coryza and cough. He remained at work, but after two weeks became aware of weakness, fever, chest pain and weight loss. Bloody sputum was noted three days before admission. The past history was positive for the usual childhood exanthemata, scarlet fever, and gonorrhea. There was also a history of joint pains and stiffness. The family history was noncontributory.

The positive findings on physical examination were limited to the chest. Dullness was present at the right base, and numerous rhonchi and râles were heard bilaterally. The heart was normal except for tachycardia and the blood pressure was 110 mm. Hg systolic and 80 mm. diastolic. The initial diagnosis of primary atypical pneumonia was confirmed by roentgen-ray which showed evidence of this condition bilaterally.

The temperature on admission was 101.2° F., the pulse was 124, and the respirations were 32. The white blood cell count was 10,200, hemoglobin was 12.8 grams, and the serology was negative. Subsequently the white count varied between 10,000 and 38,000 with up to 94 per cent polymorphonuclear leukocytes. Sputum

cultures revealed the presence of *Neisseria catarrhalis* and alpha streptococcus. Other cultures were positive for Pneumococcus of the "A" group and for Staphylococcus. No tubercle bacilli were ever obtained. The urine contained albumin on several occasions; the concentration was good and the sediment showed numerous white blood cells and occasional red blood cells. Two months after the onset of the illness an antistreptolysin titer was reported as showing 1550 units.

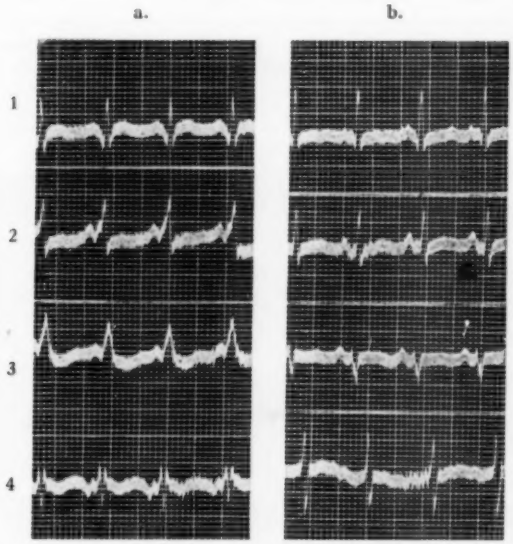


FIG. 1. *a.* Obtained on the sixth hospital day. Short P-R, long QRS pattern with rate of 136 and low-to-inverted T-waves in all leads. *b.* Made on the tenth day. Normal conduction. Rate 136, axis rotated to the left. T-waves everywhere low-to-flat.

The initial therapeutic measure consisted of the administration of 25,000 units of penicillin every three hours. On the following day the patient appeared worse and breathing was more labored. However, there were still no frank signs of consolidation. Two days later the dyspnea increased further and cyanosis was first noted. Sulfadiazine was started and the patient was put into an oxygen tent. In spite of this he suddenly went into acute vascular collapse with marked cyanosis, pulmonary edema, hyperpnea, sweating and a rapid, thready pulse. Intravenous aminophylline was given and appeared to control the seizure. On the following day the episode recurred, with respirations increasing to 60 and pulse to 160 per minute. At this time he was rapidly digitalized, kept in oxygen, and given morphine to control the tachypnea and apprehension. The cyanosis and dyspnea persisted for several days and gradually receded. During this time the patient was maintained on penicillin, cedilanid, aminophyllin, oxygen and morphine.

On the tenth day of hospitalization, although the patient felt somewhat more comfortable, roentgen-rays demonstrated extensive spread of the process bilaterally.

On the eleventh day he again went into acute collapse with evidence of gross pulmonary edema. For some time he was almost completely unresponsive but finally improved following the administration of aminophylline, coramine and oxygen by positive pressure mask.

Following the last episode of collapse, improvement was steady and no further evidence of cardiac inadequacy was ever noted. On the eighteenth day penicillin and cedilanid were discontinued and he was given bathroom privileges. There were no further setbacks and the patient proceeded to get well clinically. Subsequent roentgenographic films showed progressive clearing of the pneumonic process. No pleural or pericardial fluid was ever demonstrated and there was no enlargement, distortion or displacement of the heart. Fluoroscopy was interpreted as showing slight diminution of the cardiac excursion.

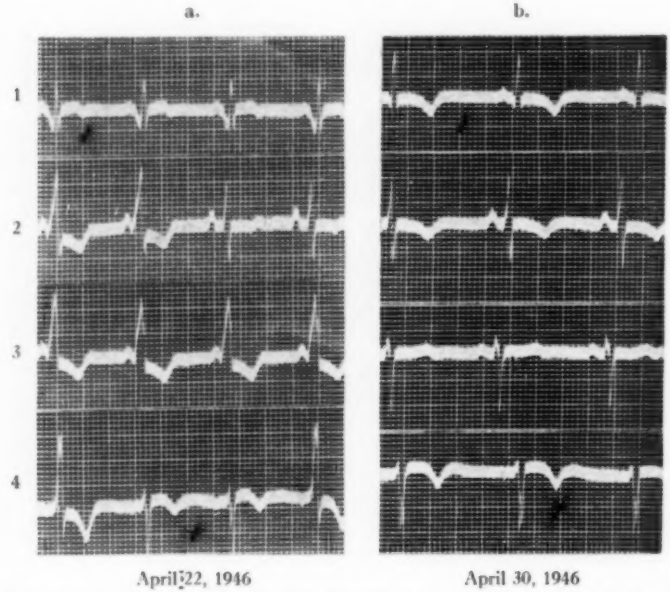


FIG. 2. *a.* Obtained on the seventeenth hospital day. Lead I: Short P–R, long QRS pattern. Lead II: The first 2 beats show abnormal conduction, the third and fourth have a normal P–R and QRS. Lead III: Abnormal throughout. Lead IVF: The first and fourth beats are abnormal; the second and third show normal conduction. However, note inverted T-waves in those beats having normal duration of QRS. *b.* Normal conduction throughout. Left axis deviation. T inverted in L1, L2 and 4F.

A long series of electrocardiograms was made beginning on the sixth day. The first of these showed marked tachycardia, low to inverted T-waves in all leads, and what appeared to be an instance of short P–R, long QRS pattern. Five days later a tracing showed normal conduction with a P–R interval of .13 second. However, the T-waves were low to flat. On the seventeenth day an electrocardiogram revealed a curious mixing of normal and abnormal impulses. Most of the ventricular com-

plexes were of the short P–R, long QRS type but a number in the second and fourth (4F) leads had a P–R interval of normal length. In those beats demonstrating a normal P–R: QRS relationship the T-waves were abnormal and were thought to represent evidence of acute myocarditis. This was the last electrocardiogram which showed any trace of abnormal impulse distribution.

On the twenty-fifth day a tracing was made which revealed a P–R interval of .12 and a QRS of .07 second. There was left axis deviation and inverted T-waves in the first, second and fourth leads. Two weeks later T_4 had become erect while the other leads remained unaltered. Over a period of time gradual erection of the inverted T-waves took place and the most recent graphs were entirely within normal limits. The last of these was made two years after the acute illness.

The patient subsequently returned to work and except for occasional joint pains has been entirely asymptomatic.

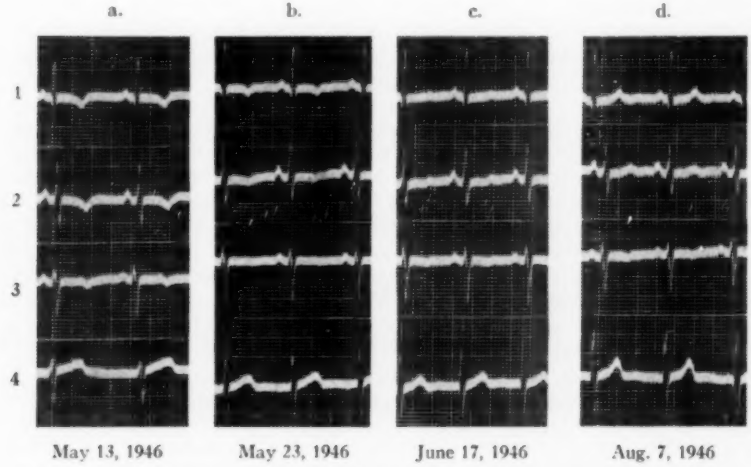


FIG. 3. Progressive recovery from myocarditis. Note gradual erection and heightening of the T-waves.

DISCUSSION

The episodes of acute failure in this patient may have resulted from either the toxic state of the myocardium or from paroxysms of tachycardia. Unfortunately no electrocardiograms were made during the attacks so that the exact mechanism remains obscure. The high white blood count and elevated antistreptolysin titer were thought to be consistent with a streptococcus infection. However, one wonders if the illness was not actually a bizarre type of rheumatic fever with pulmonary and myocardial manifestations.

Since the first electrocardiogram in this patient showing abnormal A-V conduction was obtained when myocardial involvement was already evident, one cannot be certain that the syndrome of short P-R and long QRS was present before the illness. It is possible, therefore, that the aberrant conductor began

to function after the normal mechanism had already been suppressed. With recovery it lost its temporary advantage and normal impulse distribution recurred. In this manner it would resemble the case described by Wolferth and Wood [6] in which the electrocardiographic syndrome was present during active rheumatic fever but had disappeared two years later. However, it will be recalled that partial reversion to normal P-R and QRS duration occurred when the myocarditis was at its height and that electrocardiographic evidence of myocardial involvement persisted long after all vestiges of accessory conduction had disappeared. It would appear, therefore, that a functioning aberrant pathway had been completely and permanently suppressed during the course of severe, toxic myocarditis.

Although these conclusions are warranted from the evidence in this case, it is unlikely that most instances of Wolff-Parkinson-White syndrome are ended in so dramatic a manner. It is felt that more commonly progressive vascular changes lead to diminution of irritability of the vestigial pathway to the point where it ceases to be an important agent of atrioventricular conduction.

Summary

The mechanism, physiologic activity and eventual fate of the accessory atrioventricular conductor in Wolff-Parkinson-White syndrome are discussed.

A case of Wolff-Parkinson-White syndrome is presented which was first observed during the course of an acute illness with associated myocarditis. All traces of premature ventricular excitation disappeared while electrocardiographic evidence of myocarditis was still present.

It is suggested that the accessory atrioventricular conductor was completely and permanently suppressed by the toxic process.

The author expresses his gratitude to Dr. Paul D. White for his interest in and criticism of this paper.

BIBLIOGRAPHY

1. Bodlander, J. W.: The Wolff-Parkinson-White syndrome in association with congenital heart disease. Coarctation of the aorta, Am. Heart Jr., 1946, xxxi, 785.
2. Butterworth, J. S.: The experimental production of the syndrome of apparent bundle branch block with short P-R interval, Jr. Clin. Invest., 1941, xx, 458.
3. Butterworth, J. S.: Personal communication.
4. Littmann, D., and Tarnower, H.: Wolff-Parkinson-White syndrome. A clinical study with report of nine cases, Am. Heart Jr., 1946, xxxii, 100.
5. Holzman, M., and Scherf, D.: Über Elektrocardiogramme mit verkurzter Vorhof-kammerdistanz und positiven P-Zacken, Ztschr. f. klin. Med., 1932, cxxi, 404.
6. Wolferth, C. C., and Wood, F. C.: The mechanism of production of short P–R intervals and prolonged QRS in patients with presumably undamaged hearts; hypothesis of an accessory pathway of auriculoventricular conduction (Bundle of Kent), Am. Heart Jr., 1933, viii, 297.
7. Wolff, L., Parkinson, J., and White, P. D.: Bundle branch block with short P–R interval in healthy young people prone to paroxysmal tachycardia, Am. Heart Jr., 1930, v, 685.
8. Wood, F. C., Wolferth, C. C., and Geckler, G. D.: Histologic demonstration of accessory muscular connections between auricles and ventricles in a case of short P–R interval and prolonged QRS complex, Am. Heart Jr., 1943, xxv, 454.

VITAMIN D INTOXICATION DUE TO ERTRON: REPORT OF TWO CASES *

By CHARLES K. DONEGAN, M.D., ADDISON L. MESSER, M.D., and EDWARD S. ORGAIN, M.D., F.A.C.P., *Durham, North Carolina*

THE deleterious effects of large doses of vitamin D, although well established, have not received sufficient emphasis in the therapy of those chronic conditions, notably arthritis, for which prolonged administration of the drug has been suggested.

Danowski, Winkler, and Peters [1] reported two patients suffering from vitamin D intoxication, one of whom was taking vitamin D produced by the electrical activation of heat vaporized ergosterol. In both instances there was evidence of decreased renal function, and one patient exhibited soft tissue calcification. Freeman, Rhoads, and Yeager [2] described toxic symptoms due to hypervitaminosis D in two subjects taking Ertron. The important symptoms and signs presented were lassitude, weakness, anorexia, skin eruption, involvement of the conjunctivae, renal insufficiency, anemia, and eosinophilia.

Bauer and Freyberg [3] reviewed the literature and summarized the postmortem findings in five cases of hypervitaminosis D with metastatic calcification, adding one case of their own. In four instances metastatic calcification was considered to be the cause of death. These authors found the pathological changes associated with vitamin D intoxication to consist chiefly of calcification involving the arterial vascular system and the kidneys. Kaufman, Beck, and Wiseman [4] reported a patient developing massive metastatic tissue calcification, renal insufficiency and anemia resulting in death following Ertron therapy.

We believe that intoxication from the administration of massive doses of vitamin D is more widespread than the reports in the literature appear to indicate, for the clinical picture may masquerade as renal disease or even hyperparathyroidism. The paucity of recorded instances of injurious effects points out the need for further emphasis of this syndrome.

Two patients exhibiting hypervitaminosis D due to Ertron ingestion have been observed recently. In one renal disease was prominent, while in the other hyperparathyroidism was suggested.

CASE REPORT

Case 1. History: Mrs. L. E. W., a 59-year-old housewife, was admitted to Duke Hospital on January 27, 1946, complaining of progressive weakness and lassitude of 18 months' duration and of visual disturbances for eight months. The patient was active until five years before admission at which time she developed a progressive, low-grade polyarthritis involving the hands, elbows, shoulders, back, and knees. A diagnosis of rheumatoid arthritis was made and physiotherapy was started a few months later. In January, 1941, her tonsils were removed, and this was followed by three roentgen-ray treatments to the posterior pharynx. Multiple teeth were extracted, and a submucous resection was performed in an effort to eliminate foci of infection.

* Received for publication August 28, 1947.
From the Department of Medicine, Duke University School of Medicine and Duke Hospital, Durham, North Carolina.

In March, 1943, vitamin D therapy in the form of Ertron capsules was begun at the suggestion of an arthritic friend. During 1943 she ingested 17,500,000 U.S.P. units (approximately 50,000 U.S.P. units daily); in 1944, 35,000,000 U.S.P. units (approximately 100,000 U.S.P. units daily); and in 1945, 60,000,000 U.S.P. units (approximately 150,000 U.S.P. units daily).* Because of improvement in her arthritis, physiotherapy was stopped eight months before admission and Ertron was discontinued one week before admission.

Eighteen months before admission the patient noticed the onset of lassitude, weakness, anorexia, frequency with nocturia four to five times a night, and developed an anemia which failed to respond to iron, liver therapy, and two transfusions. For eight months prior to admission there had been a gradual progression of dimness and blurring of vision, photophobia, and burning of the eyes which had not responded to treatment. For four to five months prior to admission restlessness and insomnia were present. She had lost about 60 pounds in body weight during the course of her arthritis.

Physical Examination: The temperature was 36.4° C.; the pulse was 80 beats per minute; the respirations were 20 per minute; and the blood pressure was 150 mm. of mercury systolic and 80 mm. of mercury diastolic. The patient was a chronically ill, mentally vague, sallow complexioned, 59-year-old white female manifesting evidence of marked weight loss. The eyes showed increased pigmentation and slight puffiness of the upper lids. There was a slight bilateral ptosis which was not of the sympathetic type. Paralysis of upward gaze was present, but the extraocular muscles were otherwise normal. There was bilateral hypesthesia and associated dehydration of the cornea and conjunctiva with some areas of filamentous keratitis of the cornea. Dryness of the mouth was present which was thought to be due to recent roentgen-ray therapy. The lungs were clear. The heart was normal in size and shape. The sounds were of average intensity, and there was a soft systolic murmur at the apex. The rhythm was normal. The abdomen was not remarkable. The hands revealed fusiform swelling of all the proximal phalangeal joints and the metacarpophalangeal joints. There was slight limitation of extension of the right elbow and more marked limitation of the left. The knees were slightly enlarged without limitation of movement. Several of the finger joints exhibited firm, non-tender, freely movable, subcutaneous nodules, about 1 cm. in diameter. There was a firm, non-tender movable cystic mass in the right popliteal fossa. The reflexes and sensory system were intact.

Laboratory Data: The hemoglobin was 12.2 grams per cent. The red blood cell count was 4,200,000 per cu. mm. The white blood cell count was 5,100 per cu. mm. The sedimentation rate was 43 mm. in one hour corrected (Wintrobe) and the Weltmann band was 6½. The urine revealed a trace of albumin. The blood non-protein nitrogen was 55 mg. per cent. The serum calcium was 13.4 mg. per cent; the serum phosphorus was 4.4 mg. per cent; and the serum alkaline phosphatase was 3 Bodansky units. In the two-hour phenolsulfonphthalein renal excretion test 2 per cent of the dye was excreted in two hours. The maximal concentration of the urine during the Mosenthal test was 1.009. A roentgen-ray film of the chest showed the heart and lungs to be normal. A roentgenogram of the hand showed arthritic changes about the fingers of the left hand with a large amount of calcium deposited around the third and fifth fingers. There were minimal arthritic changes in the right knee. Skull films were negative. The lumbar spine, pelvis, and the left tibia showed some loss of calcium with calcification in the blood vessels of the left leg. An electrocardiogram was within normal limits.

Course in the Hospital: The mental cloudiness cleared somewhat during her stay in the hospital, and she was discharged on the seventeenth hospital day upon a low

* The manufacturer has recommended as high as 300,000 U.S.P. units per day for at least one year.

calcium, low phosphorus diet, with ferrous sulfate, vitamin A ophthalmic ointment, and dark glasses.

Follow-up: The patient was seen during an out-patient visit in April, 1946. She reported that her nocturia had decreased to once or twice each night; there was less weakness; and her appetite and vision had improved. There had been a slight increase in the stiffness of her joints. No significant changes in the physical examination were noted.

The patient entered Duke Hospital again on the Surgical Service in May, 1946, for excision of the cystic mass in the right popliteal fossa. Microscopic examination of the cyst wall showed extensive accumulation of lymphocytes and large mononuclear cells with some fibrosis, and chemical analysis of the cyst wall was positive for cholesterol. The post-operative course was uneventful.

The patient was last seen during an out-patient visit in December, 1946. She reported general improvement with a weight gain of 15 pounds, and return of most of her former energy. There was no regression of her arthritis. Subjectively, her

TABLE I

Laboratory Findings in Case 1

	May 1944*	January 1946	February 1946	April 1946	December 1946
Hemoglobin	12 gm. %	12.2 gm. %	10.5 gm. %	9.8 gm. %	10.9 gm. %
Red blood cell count	4.4 million	4.2 million	3.2 million	3.5 million	3.7 million
White blood cell count		5,100	6,000	5,200	3,900
Sedimentation rate (Wintrobe)		43 mm./hr.		5	47 mm./hr.
Weltmann band		6.5		5	5
Blood pressure	120/70	120/70	160/90	130/70	130/80
Basal metabolic rate	−9%	−23%			
Two-hour phenolsulfonphthalein excretion test		2%	4.7%	12% and 13%	19% and 16%
Mosenthal urine conc. (maximum)		1.009			
Urine albumin	0	Trace	Trace	1+	1+
Urine microscopic	Neg.	Neg.	Neg.	Many fine gran. casts	Occ. hyaline and coarsely gran. cast
Blood NPN	55 mg. %	55 mg. %	60 mg. %	58 mg. %	52 mg. %
Blood urea nitrogen			36 mg. %	33 mg. %	32 mg. %
Blood urea ratio			60	57	62
Blood uric acid	4 mg. %	5.3 mg. %	3.9 mg. %	3.4 mg. %	4.2 mg. %
Serum bromides		Neg.			
Serum calcium	8.7 mg. %	13.4 mg. %	12 mg. %	8.8 mg. %	8 mg. %
Serum phosphorus	3.6 mg. %	4.4 mg. %	3.6 mg. %	3.1 mg. %	2 mg. %
Serum alkaline phosphatase (Bodansky units)	3.6	3			2
Serum cholesterol			267 mg. %		
Plasma proteins		7.6 gm. %			
Plasma albumin		4.1 gm. %			
Plasma globulin		3.5 gm. %			

* From the University of Virginia Hospital.

eyes felt better, but no objective improvement was disclosed on examination. In addition to her previous physical findings, examinations revealed a cystic mass over the dorsum of the left hand, and the edge of the liver and the tip of the spleen were just palpable. There were no changes in the roentgen-rays of the joints.

The laboratory findings are summarized in table 1.

Summary: Case 1 presents the picture of a patient with rheumatoid arthritis who had been taking Ertron in large doses over a prolonged period of time with the development of weakness, lassitude, metastatic calcification, disturbance of vision, lesions of the conjunctivae, and renal insufficiency. Following the discontinuance of Ertron therapy and the institution of a low-calcium regimen, the serum calcium gradually returned to normal levels. Although some amelioration of her symptoms was noted, there was no significant improvement in renal function after 11 months of observation. This very probably indicates irreversible damage to the kidneys.

Case 2. History: Mrs. L. P. H., a 56-year-old white married school teacher, was first seen at Duke Hospital September 6, 1945, complaining of low-back pain of two years' duration with drowsiness, nausea, and vomiting of three weeks' duration.

The patient had complained of low-back pain since childhood, with increasing pain and stiffness in the low-back region during the past two years. A corset gave little relief. Five months before admission the patient had stopped teaching because of increasing difficulty in moving about and since then had led a sedentary life.

Five months before admission her physician prescribed three Ertron capsules (150,000 U.S.P. units) daily, and two months before admission the dosage was increased to six Ertron capsules daily (300,000 U.S.P. units). A total of 31.5 million units of Ertron was received over a period of five months without improvement.

Three weeks before admission a bromide preparation for mild hypertension was begun. During this period the patient became progressively drowsy and developed anorexia with nausea and vomiting.

Physical Examination: The temperature was 37° C.; the pulse was 120 beats per minute; the respirations were 18 per minute; and the blood pressure was 161 mm. of mercury systolic and 88 mm. of mercury diastolic. The patient was a well-developed, well-nourished, lethargic, white woman with thick slurred speech. The optic fundi revealed minimal tortuosity of the arterioles without exudates. A 3 by 3 by 3 cm. hard mass which displaced the trachea slightly to the right was felt at the left lower lobe of the thyroid gland. The lungs were clear. The heart was slightly enlarged to the left by percussion. The rhythm was regular. The sounds were of normal intensity without murmurs. The abdomen was not remarkable. There was diffuse tenderness over the lower thoracic and lumbar spine with moderate muscle spasm. Straight leg raising tests performed upon both sides produced low-back pain.

Laboratory Data: The hemoglobin was 10 gm. per cent. The red blood count was 3,200,000 cells per cu. mm. The white blood count was 5,700 cells per cu. mm. The urine was positive for albumin but negative for sugar and sediment. The serum bromides were 100 mg. per cent. The serum calcium was 13 mg. per cent; the serum phosphorus was 2.2 mg. per cent; and the serum alkaline phosphatase was 4 Bodansky units. Blood non-protein nitrogen was 56 mg. per cent with a urea nitrogen of 39.7 mg. per cent, giving a blood urea ratio of 71. The maximal concentration of the urine during the Mosenthal test was 1.009. In the two-hour phenolsulfonphthalein renal excretion test 33 per cent of the dye was excreted, and upon repetition of the test 23 per cent of the dye was excreted.

A roentgen-ray film of the chest revealed scarring in the apices and a generalized increase in pulmonary markings. The heart was slightly enlarged to the left. A

plain film of the abdomen and a gastrointestinal series were not remarkable. Films of the lumbo-sacral spine showed extreme osteoporosis and slight osteoarthritic changes.

Course in the Hospital: The patient remained in the hospital for 30 days. During this time Ertron and bromides were discontinued, and large amounts of sodium chloride, iron, and liver extract were given. She was placed on a fracture board with a firm mattress and given daily heat and massage, strengthening exercises, and a strong low-back corset. She improved subjectively during her hospital stay, and was instructed to continue the same regimen at home.

TABLE II

Laboratory Findings in Case 2

	September 1945	November 1945	December 1945	March 1946
Hemoglobin	10 gm. %	13.2 gm. %	13.6 gm. %	15.4 gm. %
Red blood cell count	3.2 million	4.5 million	4.6 million	
White cell blood count	5,700	8,200	7,500	7,700
Blood pressure	160/95	180/100	155/100	170/90
Basal metabolic rate			+4%	
Two-hour phenolsulfonphthalein excretion test	33% and 23%		45%	73%
Mosenthal urine conc. (maximum)	1.009			1.019
Urine albumin	1+	Trace	Trace	Neg.
Urine microscopic	Neg.	Neg.	Neg.	Neg.
Blood NPN	56 mg. %	50 mg. %	44 mg. %	37 mg. %
Blood urea nitrogen	39.7 mg. %	25 mg. %	19 mg. %	16 mg. %
Blood urea ratio	71	50	46	44
Serum bromides	100 mg. %	Neg.		
Serum calcium	15 mg. %	12.6 mg. %	12.5 mg. %	10.1 mg. %
Serum phosphorus	2.2 mg. %	4.2 mg. %	2.2 mg. %	3.5 mg. %
Serum alkaline phosphatase (Bodansky units)	4		2.4	
Plasma proteins				6.9 gm. %
Plasma albumin				4.0 mg. %
Plasma globulin				2.9 gm. %

Follow-up: The patient continued this regimen at home with some improvement and returned two months later. (See table 2 for findings on this admission.) A chest film showed a slight reduction in the heart size. Roentgenograms of the spine and the right shoulder showed severe osteoporosis without cystic change. A film of the abdomen showed the kidneys to be slightly smaller than usual but no stones were visible.

It was felt that the thyroid adenoma should be removed and that the neck should be explored for the possibility of parathyroid tumor. On March 11, 1946, a subtotal thyroidectomy was performed, but no abnormal parathyroid tissue was found. Her post-operative course was uneventful.

The patient has not been available for follow-up studies since her discharge in March, 1946.

Summary: Case 2 presents the picture of a patient with low-back pain, who ingested large amounts of Ertron over a five-month period. On admission she exhibited no serious symptoms referable to Ertron poisoning; however, she was found to have severe renal impairment, an elevated serum calcium level, and a marked anemia. During the ensuing six months there was marked improvement of the renal function as illustrated by the increased excretion of the phenolsulfonphthalein dye in two hours, increased ability to concentrate the urine, and a return of the blood non-protein nitrogen and urea to standard levels. The blood calcium fell to a normal level, and the anemia disappeared. This case illustrates that serious kidney damage and disturbed calcium-phosphorus metabolism resulting from Ertron poisoning may be transitory if the clinical condition is recognized in time. In this respect case 1 and case 2 manifest sharp contrasts.

Discussion

Ertron is prepared by the electrical activation of heat vaporized ergosterol (Whittier process). The possible toxic effects have been minimized by its manufacturer * who has stressed persistently a difference in toxicity between vitamin D produced by the electrical activation of heat vaporized ergosterol (Ertron) and that produced by ultra-violet irradiation. McChesney and Messer,[5] working with dogs, found the action of Ertron and vitamin D_2 to be similar in raising the serum calcium level of the blood, decreasing the fecal excretion of calcium, and increasing the urinary output of calcium. The exact mode of action of vitamin D in hypervitaminosis D has not been explained. The effect is not simply an increased absorption. Watchorn [6] showed that, regardless of the increased absorption, the hypercalcemia and tissue calcification are not due entirely, if at all, to increased absorption, for the amounts retained in the body are actually less than normal. Shohl,[7] in reviewing the physiology of hypervitaminosis D, states that when the dose is 1,000 times the therapeutic dose the deposition of minerals at the epiphysis is made at the expense of the shaft. The balances of calcium and phosphorus then become negative, and metastatic calcification takes place. In experimental animals there is weight loss, anorexia, and diarrhea; death may occur in five to 14 days. Animals which survive may show lesions for at least six months afterwards. With diets low in either calcium or phosphorus, calcification is less severe and more delayed, but the degenerative changes are as severe as those found in animals fed on normal diets.

In all cases of hypercalcemia, hypervitaminosis D should be considered in the differential diagnosis. Hyperparathyroidism, multiple myeloma, and skeletal neoplasm are three common causes of hypercalcemia. In hyperparathyroidism with definite changes in the bones the serum alkaline phosphatase is elevated. Gutman [8] reviewed 28 cases of hyperparathyroidism with definite changes in the bones, each of which had an elevated serum alkaline phosphatase. In 24 cases the increase was twofold or greater, and in 16 cases the increase was at least fivefold.† In the two cases of Ertron poisoning herein reported the serum alkaline phosphatase varied between two and four Bodansky units. Freeman, Rhoads, and Yeager [2] are the only other authors who have reported serum alkaline phos-

* Nutrition Research Laboratories.

† The Bodansky method which Gutman utilized gives normal values of 1.5 to 4 Bodansky units.

phatase activity in Ertron poisoning. Their two patients had serum alkaline phosphatase values of 3.2 and 5.1 Bodansky units, respectively. It appears from these four cases that the absence of an elevation of serum alkaline phosphatase in Ertron poisoning to the degree that occurs commonly in hyperparathyroidism with definite bone changes may be a helpful laboratory differential diagnostic point. The history of massive vitamin D ingestion is most important in making the differential diagnosis of hypervitaminosis D in cases of hypercalcemia.

Summary

Two cases of Ertron (activated steroids, Whittier process) poisoning are reported to emphasize that the prolonged administration of massive doses of antirachitic substances may produce disturbances in calcium-phosphorus metabolism with serious renal damage. Ertron therapy, therefore, is potentially dangerous.

If massive doses of such drugs are to be used in the treatment of arthritis, frequent observations must be made upon the hemoglobin, urine, renal function tests, and calcium and phosphorus blood serum levels in order to detect early intoxication and to prevent irreversible tissue changes.

In all instances of hypercalcemia, vitamin D intoxication should be considered in the differential diagnosis.

BIBLIOGRAPHY

1. Danowski, T. S., Winkler, A. W., and Peters, J. P.: Tissue calcification and renal failure produced by massive dose vitamin D therapy of arthritis, Ann. Int. Med., 1945, xxiii, 22–29.
2. Freeman, S., Rhoads, P. S., and Yeager, L. B.: Toxic manifestations associated with prolonged Ertron ingestion, Jr. Am. Med. Assoc., 1946, cxxx, 197–202.
3. Bauer, J. M., and Freyberg, R. H.: Vitamin D intoxication with metastatic calcification, Jr. Am. Med. Assoc., 1946, cxxx, 1208–1215.
4. Kaufman, P., Beck, R. D., and Wiseman, R. D.: Vitamin D (Ertron) therapy in arthritis, Jr. Am. Med. Assoc., 1947, cxxxiv, 688–690.
5. McChesney, E. W., and Messer, F.: The metabolism of calcium and phosphorus as influenced by various activated sterols, Am. Jr. Physiol., 1942, cxxxv, 577–586.
6. Watchorn, E.: The absorption and excretion of calcium and phosphorus by rats receiving excessive doses of irradiated ergosterol, Biochem. Jr., 1930, xxiv, 631–640.
7. Shohl, A. T.: Physiology and pathology of vitamin D *in* The Vitamins, Am. Med. Assoc., Chapter xxiv, 459–474.
8. Gutman, A. B., Tyson, T. L., and Gutman, E. B.: Inorganic phosphorus, and phosphatase activity in hyper-parathyroidism, Paget's disease, multiple myeloma, and neoplastic disease of the bones, Arch. Int. Med., 1936, lvii, 379–413.

EDITORIAL

ANTICOAGULANTS IN THE TREATMENT OF CORONARY THROMBOSIS

THE high and apparently increasing frequency of coronary thrombosis and myocardial infarction in our aging population as well as the dramatically abrupt onset and high mortality has emphasized the need for more effective measures of treatment. The conventional measures now in use, which are largely only supportive and symptomatic, doubtless facilitate survival in many cases, but the average mortality of about 20 per cent during the first attack manifestly leaves much to be desired.

For the underlying pathological changes in the coronary arteries little or nothing has been accomplished, and at present not much of a curative nature can be expected. Effective prophylactic measures are also in a very nebulous state. The myocardium, however, has a remarkable capacity for recuperating and adjusting itself to such an injury if the initial insult has not been too devastating. If the infarcted area is so extensive that it quickly results in severe decompensation and congestive failure, profound shock or grave arrhythmias, death will often be inevitable. A substantial number of patients, however, survive the immediate effects of the attack to succumb later as a result of extension of the original thrombus and increase in the size of the infarcted area or of thrombosis elsewhere in the coronary arteries or other vessels or of emboli in the pulmonary or systemic arteries. Many recent studies, both clinical and pathological, have emphasized the frequency and prognostic importance of such thrombo-embolic complications. These observations naturally suggested that such complications might be averted by measures which would reduce the coagulability of the blood. Although thrombosis at the site of a vascular injury must be regarded in general as a protective mechanism which serves to avert hemorrhage, in the coronary arteries the resulting occlusion constitutes a far graver risk.

The rationale of such treatment seems to be sound. It has been shown in animal experiments, e.g. by Solandt and Best,[1] that heparin exerts such a protective action. By injecting sodium ricinoleate into an isolated section of a dog's coronary artery which was clamped off for 10 minutes following the injection, they produced a slowly progressive thrombosis and myocardial infarction in 12 of 13 animals. In a similar series of 12 animals given sufficient heparin markedly to prolong coagulation time, infarction occurred in only one. They suggested that heparin might be useful therapeutically.

There is some direct evidence in man that the coagulability of the blood is increased after myocardial infarction. It is not possible as a rule to demonstrate this convincingly by the usual methods of determining prothrombin time, using undiluted plasma. Peters et al.,[2] however, utilizing diluted (12.5 per cent) plasma, found that the prothrombin time was reduced

[1] SOLANDT, D. Y., and BEST, C. H.: Heparin and coronary thrombosis in experimental animals, Lancet, 1938, ii, 130–132.

[2] PETERS, H. R., GUYTHER, J. R., and BRAMBEL, C. E.: Dicumarol in acute coronary thrombosis, Jr. Am. Med. Assoc., 1946, cxxx, 398–402.

in 67 of 110 cases from the normal range of 85 to 100 seconds to 47 to 75 seconds. This was not always demonstrable until two to three days after the onset and was regarded as a result rather than a cause of the initial attack. It might well, however, increase the tendency to secondary thrombosis and embolism.

In some of the earlier studies on the effect of anticoagulants on thrombophlebitis in general, occasional cases of coronary thrombosis were included, but not in significant numbers. During 1946, studies were reported of three series of cases large enough to warrant some tentative conclusions.

Wright [3] reported a series of 76 cases of acute or recurrent coronary thrombosis with myocardial infarction treated with dicumarol. Of these, 43 (with 11 deaths) were complicated by multiple thromboses, multiple emboli or both, whereas 33 cases (with four deaths), seen during the first or second attack, were not so complicated. There was no control series, but he believed that the anticipated mortality in these groups, if they had not received dicumarol, would have been double that observed. In 38 of the 43 "complicated cases," no further manifestations of thrombosis or embolism were observed after treatment with dicumarol was instituted.

Nichol and Page [4] reported similar experiences in the treatment with dicumarol of 50 consecutive attacks in 44 private patients, also without controls. Although the mortality (16 per cent) was not notably reduced, all 26 cases treated during their first attack survived. In six cases that came to autopsy, no evidence of recent thrombosis or embolism was found.

The series of Peters et al.[2] included 60 controls with 13 deaths, six from embolism which was evident clinically; and 50 cases treated with dicumarol with two deaths, one from complicating renal disease. They also reported observations (utilizing diluted plasma) which confirm those of previous workers that digitalis increases the coagulability of the blood. They cite evidence such as the report of Askey and Neurath [5] that the deleterious effects of digitalis reported in cases of myocardial infarction are due to an increase in the thrombo-embolic complications rather than in ventricular fibrillation or cardiac rupture. Of 17 untreated patients (of Peters et al.) who were given digitalis because of congestive failure, nine died, chiefly from embolism. Of eight patients treated with dicumarol who were given digitalis for the same reason, one died, from associated renal disease. They believe that dicumarol not only reduced the incidence of thrombosis and embolism and lowered the mortality rate but largely eliminated the untoward effects attributed to digitalis in such patients.

In none of these series were any toxic effects noted, nor was there any significant tendency to bleed, without doubt largely because of the care with which the prothrombin time was followed.

[3] WRIGHT, I. S.: Experiences with dicumarol (3,3'methylene-bis-(4 hydroxycoumarin)) in the treatment of coronary thrombosis with myocardial infarction, Am. Heart Jr., 1946, xxxii, 20–31.

[4] NICHOL, E. S., and PAGE, S. W., JR.: Dicumarol therapy in acute coronary thrombosis; results in fifty attacks, Jr. Florida Med. Assoc., 1946, xxxii, 365–370.

[5] ASKEY, J. M., and NEURATH, O.: Is digitalis indicated in myocardial infarction? Jr. Am. Med. Assoc., 1945, cxxviii, 1016.

Although these series were neither large enough nor sufficiently well controlled to warrant any definite conclusions, the results were so promising that the Board of Directors of the American Heart Association appointed a committee to sponsor an investigation of the subject on a large scale. This was carried out coöperatively in 16 major hospitals. One thousand cases were studied, and a preliminary report covering the first 800 cases has recently been published.[6]

Patients admitted on even numbered days (368) were treated in the usual way and served as controls. Those admitted on odd numbered days (432) received dicumarol in addition. The prothrombin time was determined daily by a standard method (Link-Schapiro, with undiluted plasma) before further dicumarol was administered. In general the dose was adjusted so as to prolong the prothrombin time from the normal 15 to 17 seconds to 35 seconds or a little more (by the method used), but to avoid such excessive prolongation as would cause bleeding. This corresponds to a reduction of the prothrombin activity to from 10 per cent to 20 per cent of normal. A lesser depression of activity is believed to be therapeutically ineffective. Dicumarol was continued for 30 days and when possible for 30 days after the last episode of thrombosis or embolism. It was withheld from patients with a history of a tendency to hemorrhage or with hepatic or renal disease.

The results have been subjected to statistical analysis, and they show conclusively that dicumarol significantly lowered the mortality rate and markedly reduced the frequency of thrombotic and embolic complications.

Thus the mortality of the treated group as a whole was 15 per cent, as compared with 24 per cent in the controls. The mortality in patients who did not show thrombotic or embolic complications was not notably reduced in the treated group (12 per cent, as compared with 14 per cent in the controls), but deaths preceded by such complications occurred in 10 per cent of the controls and in only 3 per cent of the treated cases.

When analyzed by week of illness, the mortality was highest during the first two weeks, but it was substantial during the third and fourth weeks. In all four weeks the mortality rate in the treated cases was significantly lower than in the control groups. When studied with reference to age, it was found that the reduction in mortality was limited largely to patients 60 years of age or older. The incidence of thrombotic complications was reduced in treated patients under 60, but a larger number of the untreated younger patients were able to survive them.

The incidence of thrombo-embolic complications was more strikingly affected than the mortality rate. In the control group they were recognized clinically in 25 per cent of the cases, as compared with 11 per cent in the "treated" group. Of the latter, in 5 per cent the complication occurred before any anticoagulant had been given or during the first three days of treatment before an adequate effect had been secured. In only 6 per cent did such complications appear after treatment had been well established.

[6] Wright, I. S., Marple, C. D., and Beck, D. F.: Anticoagulant therapy of coronary thrombosis, Jr. Am. Med. Assoc., 1948, cxxxviii, 1074–1079.

A critical study of these failures showed that in many instances the dose of dicumarol had not been adequate to produce the requisite prolongation of the prothrombin time. Of 38 complications occurring in treated patients for whom pertinent data were available, in only four had the prothrombin time been maintained at 30 seconds or more for three days prior to the episode.

The incidence of hemorrhage was also studied. Bleeding occurred in 6 per cent of the controls and in 12 per cent of the treated group. In 5 per cent of the latter, bleeding occurred when the patient was not receiving dicumarol or was due to other causes. Of the 30 cases of bleeding attributable to dicumarol, 15 were mild and only one was severe. This relative freedom from bleeding, however, was obtained only at the cost of systematic accurate observations of the prothrombin time. Bleeding was controlled without difficulty either by injections of a vitamin K preparation or by transfusions of fresh blood.

In 14 per cent of the treated cases, heparin was given at the start to secure an immediate effect. It was not used routinely because of the technical difficulties of administration to such patients and because the incidence of thrombotic complications is relatively low before the fourth day when dicumarol should be effective.

These observations indicate that, if facilities for determining the prothrombin time are available and are utilized, dicumarol (with or without heparin at the onset) should be administered to every patient with coronary thrombosis and myocardial infarction if no specific contraindication exists. This should be done even as late as the third week or still later if thromboembolic complications occur. To be effective, however, enough dicumarol must be given substantially to prolong the prothrombin time. Half way measures are probably quite useless. These anticoagulants will not "dissolve" a thrombus which has already formed, nor do they exert any demonstrable effect on the damaged myocardium. Their only known activity, although a potent one, is to restrict extension of the original thrombus and to prevent the formation of thrombi elsewhere, particularly of mural thrombi in the ventricles, which are such a prolific source of pulmonary and systemic emboli. If determinations of the prothrombin time can not be carried out, the risk of bleeding, if effective treatment is given, must at present be regarded as prohibitive.

There are no data to suggest that this treatment reduces the incidence of subsequent attacks of coronary thrombosis after treatment is stopped.

The possibility of averting or modifying the initial attack of coronary thrombosis by means of dicumarol has not been demonstrated. Aside from bleeding, no significant toxic effects have been reported in limited numbers of patients who have received dicumarol for long periods, even from one to three years. The impossibility in most cases of predicting an attack, however, and the cost and effort involved in following the prothrombin time in large groups for protracted periods make this impracticable at present except perhaps as a major therapeutic experiment.

P. W. C.

REVIEWS

An Introduction to Gastro-Enterology. Fourth Edition, Revised and Enlarged. By WALTER C. ALVAREZ, Professor of Medicine, University of Minnesota, The Mayo Foundation, and a Senior Consultant in the Division of Medicine, the Mayo Clinic. 903 pages; 18.5 × 26 cm. *269* illustrations. Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers, New York. 1948. Price, $12.50.

Whether or not one fully agrees with Alvarez' viewpoint about every gastrointestinal problem, his lucid presentations are always intriguing. His style is conversational and, unlike most medical writers, he frequently makes use of the first personal pronoun. Although this leads to some verbosity, one never has to hesitate to understand what he means, and the informality of his discussions is refreshing.

Alvarez' Gastro-Enterology has become a classic and this fourth edition brings up to date a comprehensive review of the literature on the physiologic background of this subspecialty of internal medicine. It makes extensive reference to work on the lower animals and at the same time correlates the results with clinical observations. Very properly the author emphasizes the maximal importance of the functions, especially the motor functions, of the small intestine. Almost the first half of the book is devoted to the normal and pathological physiology of that part of the digestive tract. "The gradient theory of the polarization of the bowel," developed and popularized by the author, receives special attention, and the experimental results and arguments that are presented are most convincing. On the other hand, many problems are left unsolved, only the established facts and theories being presented, and this is done in such a way as to be highly stimulating to the clinical investigator.

An exhaustive bibliography is appended and the 186 illustrations include photographs of the important contributors to our knowledge of the subject. The book is highly recommended and should be in the hands of every student, teacher, investigator and practitioner of internal medicine, whether or not his interests are primarily in gastrointestinal disease. It will be found particularly helpful as a background for the researches of the younger gastroenterologist.

T. GRIER MILLER, M.D.

Cornell Conferences on Therapy. Volume III. Edited by HARRY GOLD, M.D., Managing Editor, DAVID P. BARR, M.D., MCKEEN CATTELL, M.D., EUGENE F. DUBOIS, M.D., WALTER MODELL, M.D., and RALPH R. TOMPSETT, M.D. 337 pages; 14 × 21 cm. The Macmillan Company, New York. 1948. Price, $3.50.

If the analogy is not scrutinized too closely, this book bears the same relation to a textbook of medicine as an historical novel to a textbook of history. It is not a reference book, and it gives pleasure as well as information. It is the third of a series of Medical Annuals of great value and popularity.

Like its two prototypes, this volume contains verbatim reports of a number of conferences held in recent years at the Cornell University Medical Center. All those incorporated in this volume have appeared either in the American Journal of Medicine or in the New York State Medical Journal between May 1944 and March 1948.

The stated purpose of the Cornell conferences has been "to stimulate interest in rational therapy," and to bridge the artificial gap between Pharmacology and Therapeutics by bringing clinicians and pharmacologists together in active debate. Each conference follows a pattern: an expert in the field introduces the subject of the day, and this is followed by free and informal discussion by the multivalent assembly. With this form of presentation, no matter how carefully the material is selected, there is bound to be included a certain amount of useless and uninformative matter. Some

may wonder if it is justifiable to make such inclusive material into a book; in the same number of pages half as much information again could be compressed. But this apparent waste of space is more than made up for by the ease and pleasure with which the whole book is read. Its form endows it with a natural, informal and varying style. Many gems of practical wisdom fall from the lips of the expert engaged in impromptu discussion, which never seem to find their way into the pages of a formal text. Only in a book of this kind is the experience of specialists pooled and compared, and it is not only helpful to observe where they agree but also where they disagree; for where experts differ there is comfort in our own bewilderment.

The conferences in this volume deal with such therapeutic agents as streptomycin, protein hydrolysates, BAL and the cathartics; and with such therapeutic problems as congestive heart failure, pneumonia, barbiturate poisoning, thrombophlebitis, alcoholism, and infections of the urinary tract. More general subjects such as the dose of a drug and the management of pain due to muscle spasm are also each accorded a session. Such a book will inevitably cater to a wide range of satisfied readers.

H. J. L. M.

The Treatment of Malignant Disease by Radium and X-Rays. By RALSTON PATERSON. 622 pages; 17 × 25 cm. The Williams and Wilkins Co., Baltimore. 1948. Price, $11.00.

This book is primarily for radio-therapists. The author confines his work to the treatment of malignant disease as carried out at Christie Cancer Hospital and Holt Radium Institute. There is a fine description of the principles of radiation therapy, together with the necessary technical factors, for the intelligent use of radiation. Dr. Paterson gives us the benefit of his great experience with radium. Not only does he describe the use of radium, but also gives minute details for the construction of radium applicators and radium molds. In the experience of the Institute only four types of cancer are considered curable, i.e., having an appreciable five year survival rate: cancer of the skin, the lip, uterus (both body and cervix), and breast.

Every case presented for treatment is put into one of four classes: curable, treatable, palliative, and those in which treatment is contraindicated. Dr. Paterson feels that most physicians understand the application of the last three methods, but that in the curable class physicians must be made to realize that radical radiation methods should be used. When surgery is used in malignancy, nothing short of radical surgery is now accepted even though it entails many risks—for this reason the cure rate after radical surgery is now better than that in the days before this radical principle was accepted. If the same risks be accepted for radical radiation therapy our "cure rates" will improve.

Included is a plan of organization for a radiation institute equipped to handle 1500 new cases a year, plus follow-up of all old cases.

The book ends with an outline of the present status of research into the manner by which radiations produce their biological effect.

A. G. S.

Crystalline Enzymes. 2nd Ed. By JOHN H. NORTHROP, MOSES KUNITZ, and ROGER M. HERRIOTT. 352 pages; 16 × 24 cm. Columbia University Press, New York. 1948. Price, $7.50.

The material in this volume, as in the first edition, has been limited to studies made in the Laboratory of General Physiology at the Rockefeller Institute for Medical Research and to closely related work. In the ten years since the earlier edition, the number of enzymes which have been isolated and crystallized has reached 35 and the controversy over the protein nature of enzymes has been largely settled. The chemi-

cal structure responsible for activity and the question as to whether or not prosthetic groups are necessary is, however, still under discussion.

Much new material has been included in this edition. The preparation and properties of two enzymes, ribonuclease and hexokinase, and of crystalline diphtheria antitoxin have been discussed in detail. The solubility method for the determination of the purity of proteins and its superiority over electrophoresis and ultracentrifugation for the detection of more than one protein component is discussed. The formation of proteins, of enzymes, and of virus is considered as one general problem—the synthesis of proteins. The authors have presented a critical analysis of the various possible synthetic reactions for proteins and have suggested a working hypothesis for their synthesis.

This highly specialized volume is extremely valuable as a reference for those interested in this field.

M. A. A.

Investigations on Agonal Acidosis. By IB FABRICIUS HANSEN. 135 pages; 18.5 × 26.5 cm. Povl Branner, Copenhagen, Denmark. 1948. Price, $3.00.

"Investigations on Agonal Acidosis" is the report of studies on the biochemical changes in the blood during the agonal state. Blood was obtained from 38 adult patients either premortally or by heart puncture immediately after death. Patients with diabetes or in uremic coma were excluded as the author was interested in the frequency of agonal acidosis in conditions other than those usually associated with acidosis. The following determinations were done: pH, CO_2 content, chloride, sulfate, phosphate, protein, lactic acid, acetone, pyruvic acid, total base, non-protein nitrogen, urea nitrogen, amino acids, creatinine, guanidine, oxygen capacity, oxygen content.

A fall in the pH of the blood to below pH 7 was not uncommon and occasionally this may have been the direct cause of death. The plasma bicarbonate was reduced in only about a third of the cases. An increase in lactic acid appeared as a constant agonal phenomenon while increases in sulfate, phosphate and "undetermined acids" occurred frequently. There was no definite trend in plasma chloride. Most cases showed an agonal azotemia with non-protein nitrogens ranging from 26 to 216 mg. per cent, and an increase in both amino acid nitrogen and creatinine.

This series of results constitutes the first comprehensive series of determinations of blood constituents during the agonal state and should serve as a foundation for further studies along these lines.

M. A. A.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Atlas of Human Anatomy, Descriptive and Regional. Volume I: Osteology, Arthrology, Myology. By M. W. WOERDEMAN, M.D., F.R.N.A.Sc., Professor of Anatomy and Embryology and Director of the Department of Anatomy in the University of Amsterdam. 512 pages, plus 18 pages index; 26 × 18 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $12.50.

Blood Clotting and Allied Problems: Transactions of The First Conference, February 16–17, 1948, New York, New York. 179 pages; 23 × 15.5 cm. (loose-leaf, paperbound). 1948. Josiah Macy, Jr., Foundation, New York. Price, $3.25.

The Child in Health and Disease: A Textbook for Students and Practitioners of Medicine. By CLIFFORD G. GRULEE, M.D., Rush Professor of Pediatrics, University of Illinois, etc., and R. CANNON ELEY, M.D., Associate in Pediatrics and Communicable Diseases, Howard University Medical School, etc. 1066 pages; 26 × 18 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $12.00.

Cornell Conferences on Therapy—Volume III. Edited by HARRY GOLD, Managing Editor, DAVID P. BARR, M.D., MCKEEN CATTELL, M.D., EUGENE F. DUBOIS, M.D., WALTER MODELL, M.D., and RALPH R. TOMPSETT, M.D. 337 pages; 21 × 14 cm. 1948. The Macmillan Company, New York. Price, $3.50.

Experimental Immunochemistry. By ELVIN A. KABAT, Ph.D., Associate Professor of Bacteriology, College of Physicians and Surgeons, Columbia University and the Neurological Institute, New York; and MANFRED M. MAYER, Ph.D., Associate Professor of Bacteriology, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore. With a Foreword by MICHAEL HEIDELBERGER, Ph.D., Professor of Biochemistry, College of Physicians and Surgeons, Columbia University, New York. 575 pages; 24 × 15.5 cm. 1948. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $8.75.

Factors Regulating Blood Pressure: Transactions of the Second Conference, January 8–9, 1948, New York, New York. Edited by B. W. ZWEIFACH and EPHRAIM SHORR, Department of Medicine, Cornell University Medical College, New York. 170 pages; 23 × 16.5 cm. (loose-leaf, paper-bound). 1948. Josiah Macy, Jr. Foundation, New York. Price, $2.75.

The Hormones: Physiology, Chemistry and Applications. Volume I. Edited by GREGORY PINCUS, Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts, and KENNETH V. THIMANN, Harvard University, Cambridge. 886 pages; 23.5 × 15.5 cm. 1948. Academic Press, Inc., New York. Price, $13.50.

The Modern Management of Gastric and Duodenal Ulcer. Edited by F. CROXON DELLER, M.D., M.R.C.P. 227 pages; 23 × 16.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $5.50.

The Parathyroid Glands and Metabolic Bond Disease: Selected Studies. By FULLER ALBRIGHT, A.B., M.D., Associate Professor of Medicine, Harvard Medical School, etc., and EDWARD C. REIFENSTEIN, JR., A.B., M.D., F.A.C.P., Consultant-in-Charge, Department of Clinical Investigation, Sloan-Kettering Institute of Cancer Research, Memorial Hospital Cancer Center, New York, etc. 393 pages; 23.5 × 15.5 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $8.00.

The Renal Origin of Hypertension. By HARRY GOLDBLATT, M.D., C.M., Director, Institute for Medical Research, Cedars of Lebanon Hospital, etc. 126 pages; 23.5 × 15.5 cm. 1948. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $2.75.

Textbook of the Rheumatic Diseases. Edited by W. S. C. COPEMAN, O.B.E., M.D., F.R.C.P., Physician to the Rheumatism Department and Lecturer in the Medical School, West London Hospital, etc. 612 pages; 24.5 × 17 cm. 1948. The Williams & Wilkins Company, Baltimore. Price, $12.50.

COLLEGE NEWS NOTES

30th Annual Session

Hotel Accommodations

Officers, Regents, Governors and Committeemen of the College, and Speakers on the Program of the 1949 Annual Session should apply for their hotel accommodations at once, if they have not already done so, to Mr. E. R. Loveland, Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

Instructions and application forms for reserving hotel rooms have been mailed to all members of the College. All who plan to visit New York City for the Annual Session and who have not yet reserved their rooms are urged to send their applications without delay to the Housing Bureau, The American College of Physicians, care of New York Convention Bureau, 500 Park Ave., New York 22, N. Y.

Attendance by Associates at Annual Session

Attendance at one or more Annual Sessions by Associates before their proposal for advancement to Fellowship is prescribed by regulations of the Board of Regents of the American College of Physicians. This regulation was temporarily discontinued during World War II from 1942 to 1946, because it became obviously impossible for Associates in the armed services to attend and because the Annual Sessions were not held during part of that time. The regulation is again in full effect. It is maintained that an Associate must display an abiding interest in the College and in internal medicine or its allied branches. There is no better way in which such an interest can be displayed than by attendance at the College's Annual Sessions, accepted as the most important postgraduate week in the field in North America.

1949 A. C. P. Directory

It is important that members send promptly to the College Headquarters their pre-publication orders for the 1949 Directory of the American College of Physicians, if they have not already done so and wish to reserve copies. The Board of Regents' authorization to prepare and print the Directory for distribution next autumn is contingent upon the receipt of at least 2,000 pre-publication orders. A printed order form was mailed to all members of the College early in January. The early return of these order forms will enable the Headquarters staff to begin preparations for compiling the Directory without delay.

No Directory has been published by the College since 1941. Membership Rosters, and Supplements thereto have been distributed but these lack the biographical data which make the Directory of great usefulness to the members as well as institutions and medical organizations. The pre-publication price to members of the College will be $4.00; to non-members, institutions and others, $5.00.

Regional Meetings of the American College of Physicians

The *North Carolina* Regional Meeting of the College was held at the Duke University Hospital, Durham, on December 3, 1948, with a dinner at the Washington Duke Hotel. A fine attendance was experienced at this meeting which was held under the Governorship of Paul F. Whitaker, M.D., F.A.C.P., Kinston, and planned by Edward McG. Hedgpeth, M.D., F.A.C.P., chairman of the program committee, Chapel Hill, and J. Lamar Callaway, M.D., Associate, chairman of local arrangements, Durham.

The guest speakers in the evening were President Walter W. Palmer, New York City, and Mr. E. R. Loveland, Executive Secretary, Philadelphia. The following papers were presented at the Afternoon Session:

Myocardial Contusion: Report of a Case with Autopsy.
MONROE T. GILMOUR, M.D., F.A.C.P., and HORACE H. HODGES, M.D. (Associate), Charlotte.

Clinicopathologic Conference.
DAVID T. SMITH, M.D., F.A.C.P., WILEY D. FORBUS, M.D. (by invitation) and H. LEE HOWARD, M.D. (by invitation), Durham.

Panel Discussion: Jaundice.
Physiology: A. T. MILLER, JR., M.D. (by invitation).
Pathology: R. WAYNE RUNDLES, M.D. (by invitation) and LELAND D. STODDARD, M.D. (by invitation).
Differential Diagnosis: ARTHUR J. FREEDMAN, M.D. (Associate), Greensboro.
Therapy: KENNETH D. WEEKS, M.D. (Associate), Rocky Mount.

Prolapse of the Gastric Mucosa Through the Pyloric Canal into the Duodenum.
I. H. MANNING, JR., M.D., F.A.C.P., Durham.

A meeting for the *District of Columbia and Maryland* was held on February 19, 1949, at the Medical Society of the District of Columbia, Washington, D. C., under the chairmanship of Wallace M. Yater, M. D., F.A.C.P., Governor for the District. Drs. Walter W. Palmer, New York City, and George Morris Piersol, Philadelphia, President and Secretary-General of the College, respectively, and Mr. E. R. Loveland, Executive Secretary, Philadelphia, were scheduled to be guest speakers. The detailed program of the meeting had not been received at the time this notice was written.

Nebraska members of the College held their Regional Meeting at the Paxton Hotel, Omaha, on February 19, 1949, under the Governorship of Joseph D. McCarthy, M.D., F.A.C.P., of that city. While copy of the program of this meeting had not been received when this notice went to press, Walter L. Palmer, M.D., F.A.C.P., Chicago, Chairman of the Board of Governors, had agreed to be the dinner speaker.

Announcement of the meeting of the *Virginia* Section of the College called the members to assemble at Norfolk, Va., on February 23, 1949. The Treasurer of the College, William D. Stroud, M.D., F.A.C.P., Philadelphia, was to be the guest speaker; the scientific program was not known at the time of writing. A. Brownley Hodges, M.D., F.A.C.P., Norfolk, is currently serving as chairman of the Section, and James F. Waddill, M.D., F.A.C.P., Norfolk, as secretary. W. P. Adams, M.D., F.A.C.P., Norfolk, was chairman of the Program Committee for the meeting.

NEW LIFE MEMBERS

The following Fellows of the College have become Life Members. (Listed in the order of subscription. Subscriptions received up to and including January 14, 1949.)

Dr. Aaron Arkin, Chicago, Ill.
Dr. Arden Freer, Washington, D. C.
Dr. Estelle E. Kleiber, New Brunswick, N. J.
Dr. John A. Kolmer, Bala-Cynwyd, Pa.
Dr. Francis G. Blake, New Haven, Conn.
Dr. Eliot E. Foltz, Evanston, Ill.
Dr. Robert E. Driscoll, Chicago, Ill.
Dr. Lyman H. Hoyt, Boston, Mass.

Dr. Charles H. Drenckhahn, Urbana, Ill.
Dr. Raymond Hussey, Detroit, Mich.
Dr. Samuel Waldman, Brooklyn, N. Y.
Dr. Milton D. Bosse, Pitcairn, Pa.
Dr. Donald S. Smith, Pontiac, Mich.

Correction to December, 1948, News Notes

In the list of new elections to Associateship and Fellowship in the American College of Physicians, published in the December News Notes Section, the name of Dr. Joseph Post, New York, N. Y., a newly elected Fellow, was inadvertently omitted.

Library Contribution

Grateful acknowledgment is made of the kindness of Louis F. Bishop, Jr., M.D., F.A.C.P., New York, N. Y., in contributing to the College Library a copy of the biography of his father, a late Fellow of the College, entitled "Hope in Heart Disease, The Story of Louis Faugeres Bishop, M.D.," by Ruth V. Bennett, published by Dorrance & Company, Philadelphia, 1948.

The 1949 meeting of the Southern Medical Association will be held next autumn at Cincinnati, Ohio, under the presidency of Oscar B. Hunter, M.D., F.A.C.P., Washington, D. C.

Postgraduate Course on Diabetes

The Frank E. Bunts Educational Institute and Cleveland Clinic will present a continuation course for physicians entirely devoted to the diagnosis and management of diabetes and its complications. The course will be held on March 17, 18, and 19. Drs. Henry T. Ricketts of Chicago, John S. L. Browne of Montreal, and H. L. C. Wilkerson of the United States Public Health Service will be the out-of town guest speakers. Dr. E. Perry McCullagh is director of the course. In addition to the regular faculty of the Institute several prominent Cleveland physicians will give lectures.

Inquiries regarding the complete program and registration can be addressed to the Director of Education, Frank E. Bunts Educational Institute, 2020 East Ninety-third Street, Cleveland 6, Ohio.

Specialty Board Notices

American Board of Internal Medicine, William A. Werrell, M.D., Asst. Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. Oral examinations, for which the closing date for receipt of applications was January 2, 1949, will be held in New York City, March 23, 24, and 25, before the 1949 Annual Session of the American College of Physicians, and in Philadelphia on June 1, 2, and 3, before the Annual Convention of the American Medical Association. The 1949 written examination will be given on October 17, 1949, the closing date for applications being May 1.

The American Board of Pediatrics, Inc., John McK. Mitchell, M.D., Executive Secretary, 6 Cushman Rd., Rosemont, Pa. The next oral examinations will be given on April 22, 23, and 24, 1949, at Baltimore, Md.

The American Board of Physical Medicine, Robert L. Bennett, M.D., Secretary-Treasurer, 30 N. Michigan Ave., Chicago 2, Ill. The examination period will be immediately prior to the Annual Convention of the American Medical Association, June 4 and 5. Applications must be complete and in the hands of the Secretary-Treasurer three months prior to this date.

THE AMERICAN BOARD OF RADIOLOGY, B. R. Kirklin, M.D., Secretary-Treasurer, Mayo Clinic, Rochester, Minn. *Memorandum on Certification of radiation physicists:* Beginning January 1, 1949, The American Board of Radiology will examine and certify physicists as radiation physicists. Three types of certificates will be granted: (1) Radiological Physics; (2) X-ray and Radium Physics; (3) Medical Nuclear Physics; (2) and (3) are both included in (1).

Each applicant for any one of the certificates in radiation physics will be required to meet the following standards: (*a*) Satisfactory moral and ethical standing; (*b*) That he holds himself to be a specialist in the category of physics designated in his application; (*c*) That he be a citizen of the United States or Canada. Candidates from other countries must be permanent residents of that country and native citizens thereof; (*d*) That he holds a degree of Bachelor of Arts or its equivalent and has majored in physical science or engineering; (*e*) That he be a member of the American Physical Society or similar organization; (*f*) That after graduation from college he has had at least one year postgraduate experience in radiation physics or in a radiation physics laboratory.

(*g*) Candidates for examination in Radiological Physics in addition to requirements specified in paragraphs (*a*), (*b*), (*c*), (*d*), (*e*) and (*f*) must have had at least one year of experience in association with a Department of Radiology approved by the Board and throughout one of the two years specified must have had experience in medical application of artificial radioactive materials.

Each candidate shall submit with his application personal records of calibrations of one low voltage and one high voltage x-ray apparatus, personal records of one x-ray protection survey and one protection survey for radioactive materials.

(*h*) Candidates for examination in X-ray and Radium Physics in addition to requirements specified in paragraphs (*a*), (*b*), (*c*), (*d*), (*e*) and (*f*) must have had at least one year of experience in association with a Department of Radiology approved by the Board. With the application he must submit records of personal calibration of one low voltage and one high voltage x-ray apparatus and personal records of one x-ray protection survey and one personal protection survey for radium.

(*i*) Candidates for examination in Medical Nuclear Physics in addition to requirements specified in paragraphs (*a*), (*b*), (*c*), (*d*), (*e*) and (*f*) must have had one year of experience in physical procedures relative to medical application of radioactive materials.

(*j*) Applications shall be endorsed by a Diplomate of the American Board of Radiology and a Diplomate in Radiological Physics who have personal knowledge of the experience, training, moral and ethical standing of the applicant and that he is qualified to take an examination.

(*k*) A fee of $25.00 shall accompany the application which will be refunded if the application for examination is not accepted.

(*l*) Applications shall be submitted to the Secretary of The American Board of Radiology. He shall forward them to the Credentials Committee on Radiological Physics to be appointed by the Board, who shall decide about the candidate's fitness to be examined. Those approved for examination shall be informed by the Secretary of the Board when and where to appear.

Examinations will usually be conducted at the time and place of the regular or special meetings of the American Board of Radiology.

Examinations in radiation physics shall be oral, though practical or written examinations may be required. Examinations will be designed to test the candidate's knowledge and his fitness to practice physics in the category for which he applies. Accordingly, the examination may include questions regarding the structure of matter, construction and operation of x-ray apparatus, the use of radiation measuring instruments, determination of radiation quantity and quality, protection from x-rays, radium and artificial radioactive substances, preparation of radioactive applicators,

determination of dosages of x-rays, radium and radioactive substances and other questions relative to the category in which the candidate applies.

Candidates who fail an examination shall not be admitted to another examination until one year has elapsed. They must request reëxamination at least sixty days prior to the next meeting of the Board and pay an additional fee of $10.00.

A diploma may be revoked if in the opinion of the Board a mis-statement of fact has been made in the application or any other communication to the Board or its representatives, or for expulsion from a scientific society for misconduct. Under such circumstances the diplomas must be returned to the Board and the name of the individual shall be omitted from the Registry of Diplomates.

Amendments Proposed to the Constitution and By-Laws

The Board of Regents of The American College of Physicians on November 7, 1948, formally adopted a resolution recommending the following amendments to the Constitution and By-Laws, to provide for Honorary Fellows.

Constitution, Article IV, to be amended by changing the introductory sentence to read "Members of The American College of Physicians shall be of three classes: (a) Fellows; (b) Masters; and (c) Honorary Fellows."

By adding a new Section to Article IV as follows: "(c). Honorary Fellows. Honorary Fellows shall be internists, members of the medical profession of countries other than the United States or Canada, who on account of personal character, positions of honor and influence, or eminence in the practice of internal medicine or in research, shall be recommended by the Committee on Masterships to the Board of Regents. Honorary Fellows shall not have the right to vote or to hold office."

Article IV, Section (b), shall be amended by reversing the order of the words "influence and honor" to read "honor and influence."

By-Laws, Article VI, the title to be amended to read, "Election of Masters and Honorary Fellows"; also by numbering the first paragraph "(a)", and adding paragraph "(b). The Committee on Masterships may also present to the Board of Regents nominations for the election of Honorary Fellows. Not more than two Honorary Fellows shall be elected in any calendar year."

These amendments will be presented for action by the Fellows and Masters of the College at the Annual Business Meeting at New York City on March 31, 1949.

OBITUARIES

DR. HUGH S. CUMMING

Hugh Smith Cumming, M.D., F.A.C.P., distinguished former Surgeon General of the U. S. Public Health Service, died at his home in Washington, D. C., on December 20, 1948.

Dr. Cumming was born at Hampton, Va., August 17, 1869. He attended the University of Virginia Department of Medicine and received his degree in 1893. The following year he served as house doctor in St. Luke's Hospital, Richmond, and received a second M.D. degree from the University College of Medicine (Richmond). He then obtained a commission as Assistant Surgeon in the U. S. Marine Hospital Service, later designated the U. S. Public Health Service.

During the years before his first appointment as Surgeon General in 1920, Dr. Cumming's outstanding career provided him with an experience in important national and international problems of public health. The subjects on which he became an authority included tropical diseases, quarantine inspection, bubonic plague, pollution of tidal waters, sanitation, industrial medicine and public health administration. His assignments took him to New York, San Francisco, Cape Charles, to Cannes and Yokohama and many other widely separated cities. During World War I, Dr. Cumming served in the Office of the Surgeon General of the Navy, and in 1918 went to France for sanitary studies at camps and ports.

Dr. Cumming served as Surgeon General from 1920 to 1936. Among the accomplishments of his administration are the completion of the national quarantine system, reorganization and expansion of the Service's staff and its hospital facilities, establishment of a national leprosarium and a Division of Mental Hygiene, assignment of medical officers to examine prospective immigrants at American Consulates abroad, development or expansion of research into problems important to industrial and public health, construction of two hospitals for narcotic addicts, and the successful developments which culminated, prior to his retirement, in the Congressional appropriations making possible the construction of the present National Institutes of Health.

Dr. Cumming was director of the Pan American Sanitary Bureau from 1920 to 1947 and contributed to its growth in usefulness. He was also a president of the Office International d'Hygiene and a vice president of the League of Nations Health Section.

Recognition of Dr. Cumming's contributions was not lacking. He was awarded honorary degrees of Sc.D. by the University of Pennsylvania in 1930 and LL.D. by Yale University in 1933, the Hartley Medal of the National Academy of Sciences in 1936, the Gorgas Medal and Prize of the Association of Military Surgeons of the United States, and the William Freeman Snow Award. He was commander of the Legion of Honor of France, and, with Star, of Poland Restored, and had been honored by Peru, Ecuador, Chile, Mexico, Cuba, Colombia and the Dominican Republic.

Dr. Cumming was a former president of the American Public Health and Southern Medical Associations, of the Association of Military Surgeons of the United States, and of the Gorgas Memorial Institute of Tropical and Preventive Medicine, an honorary fellow of the American Colleges of Surgeons and of Dentists and of the Canadian Public Health Association, and a member of the American Medical and Hospital Associations, Alpha Omega Alpha, Phi Beta Kappa, and other societies. Elected to Fellowship in the American College of Physicians in 1923, Dr. Cumming gave it service for many years as a member of its Board of Governors while he was Surgeon General.

DR. PAUL SCOTT HANSEN

Dr. Paul Hansen was born in Columbus, Ohio, October 16, 1910, and died September 26, 1948, at the Santa Barbara General Hospital, Santa Barbara, Calif., of poliomyelitis.

He received his Bachelor of Science degree from Harvard University in 1931, and then attended Northwestern University Medical School where he received his M.D. degree in 1938.

Dr. Hansen was a diplomate of the National Board of Medical Examiners and the American Board of Internal Medicine; he was a member of the American Medical Association and was elected to associateship in the American College of Physicians during the 1948 San Francisco meeting. He was formerly on the faculties of the University of Pennsylvania School of Medicine and the Yale University School of Medicine. During World War II Dr. Hansen served as a captain with the 15th Evacuation Hospital in Africa, Sicily and Italy. He was separated from the service as a major after 33 months of service overseas. During the time Dr. Hansen practiced in Santa Barbara, he was consultant on blood diseases at the Santa Barbara Clinic, and was affiliated with the Santa Barbara Cottage Hospital and the Santa Barbara General Hospital.

Dr. Hansen was a very fine and able physician, and will be greatly missed by all who knew him.

LELAND HAWKINS, M.D., F.A.C.P.,
Governor for Southern California

DR. GEORGE J. KASTLIN

The untimely death of George Jacob Kastlin, M.D., F.A.C.P., on December 31, 1948, at the age of 48, is a tragic loss to his professional colleagues and his many friends. At the time of his death, Dr. Kastlin was Associate Professor of Medicine in the University of Pittsburgh, senior staff physician to the Presbyterian and St. Margaret's Memorial Hospitals, consulting hematologist to St. John's General Hospital, Montefiore Hospital and Pittsburgh Diagnostic Clinic, senior consultant to the Veterans Administration Hospital, Aspinwall, and associate medical director of the Pittsburgh Skin and Cancer Foundation.

Dr. Kastlin was born in Savanna, Ill., July 11, 1900. He received the degree of B.S. from the University of Wisconsin in 1922, and M.D. from the University of Pennsylvania in 1924. He interned at the Mercy Hospital, Pittsburgh, 1924–25, and was a resident in pathology at the Toronto General Hospital, 1925–26. In 1926–27 he held the position of assistant clinical pathologist at the State of Wisconsin General Hospital and instructor in clinical pathology in the University of Wisconsin Medical School. In 1927, he returned to Pittsburgh where he established a wide reputation as a specialist in diseases of the blood and lymph glands.

During the war he served in the Medical Corps, A.U.S., 1942–46, separating with rank of Colonel.

Dr. Kastlin was a member of the Allegheny County Medical Society and the Medical Society of the State of Pennsylvania, and a fellow of the American Medical Association. He was a member of the American Society of Clinical Pathologists, American Association of Pathologists and Bacteriologists, the Clinical-Pathological Society of Pittsburgh, the Toronto Academy of Medicine, and, since 1931, was a fellow of the American College of Physicians.

Dr. Kastlin combined, to an unusual degree, an accurate knowledge of the basic sciences with great clinical intuition, so that he was especially successful in the treatment of those suffering with glandular and hematologic disorders. He was a clear

thinker and a vivid lecturer and took a very active part in symposia and postgraduate sessions. In particular, he made outstanding contributions to the courses in internal medicine given in Pittsburgh by the American College of Physicians.

Above all, George Kastlin was singularly free from petty envy or jealousy. He was kind and generous, and always ready to share his technical facilities and knowledge with his colleagues. He will be sadly missed by a host of friends and admirers.

R. R. Snowden, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. THEOPHIL KLINGMANN

Theophil Klingmann, M.D., F.A.C.P., of Ann Arbor, Mich., died there on September 19, 1948. Born in that city in 1868, Dr. Klingmann was a graduate of the University of Michigan (Ph.C. and M.D., 1892). He served as pathologist to the Michigan State Hospital for the Insane, 1901–05, and as instructor in neuropsychiatry and demonstrator in neuropathology, University of Michigan Medical School, 1901–18. He undertook postgraduate studies in Leipzig and Berlin, 1906–08; in Vienna, 1910; and in Philadelphia, in 1912. Formerly medical director of Mercywood Psychiatric Hospital, Dr. Klingmann was also chief of the Division of Neuropsychiatry in St. Joseph's Mercy Hospital.

Dr. Klingmann was a past president of the Washtenaw County Medical Society, past vice president of the Detroit Society of Neurology and Psychiatry, a member of the American Psychiatric Association, Association for Research in Nervous and Mental Disease, and a fellow of the American Medical Association. He was one of the early members of the American College of Physicians, having been elected to fellowship in 1919.

DR. JOHN J. MOREN

John J. Moren, M.D., F.A.C.P., died on October 26, 1948, at the Veterans Administration Hospital, Louisville, Ky., of pleurisy with effusion. He was in his 78th year.

Born in London, Ky., he attended Center College and the University of Kentucky. He had an M.D. degree from the Louisville Medical College in 1894, and an M.D. degree from the Hospital College of Medicine, Louisville, in 1895. He immediately specialized in neurology, taking postgraduate work in Philadelphia, New York, Berlin and London. He was engaged in the practice of medicine in Louisville from 1894 to 1941.

Dr. Moren was a member of the faculty of the University of Louisville School of Medicine for 40 years, and was Clinical Professor of Neurology and Head of the Department of Neurology from 1928 until 1940 when he became emeritus. He served overseas as a Major in the U. S. Army Medical Reserve Corps during World War I. He was President of the Jefferson County Medical Society in 1906, and of the Kentucky State Medical Association in 1915. He had been a fellow of the American College of Physicians since 1917.

Dr. Moren was the epitome of the physician, a kindly, courteous, gentlemanly scholar, throughout his entire lifetime. Up until his death, he constantly kept abreast of new developments in medicine in general as well as in his own particular field. He was a most unusual teacher who succeeded in teaching sound medical principles along with his neurology. His modest seeking after knowledge was an inspiration to generations of medical students who profited by their contact with him in many more ways than simply from the neurology he taught.

William K. Keller, M.D., F.A.C.P.

DR. ROBERT M. MORRISON

Robert Mehard Morrison, M.D., F.A.C.P., of Youngstown, Ohio, died November 19, 1948. Dr. Morrison was born in Wurtemburgh, Pa., in 1872 and received his medical education at the University of Pittsburgh School of Medicine, from which he received his degree in 1895. For many years a consulting physician and subsequently Chairman of the Board of Youngstown Hospital, Dr. Morrison practiced general medicine with emphasis on internal medicine.

Dr. Morrison was a member of the Mahoning County, Ohio State and American Medical Associations. He became a fellow of the American College of Physicians and a member of The American Congress on Internal Medicine in 1920.

DR. JOSEPH H. BRYAN

Joseph Harker Bryan, M.D., of Asbury Park, N. J., died October 21, 1948.

Dr. Bryan was born in Newark, N. J., December 15, 1865. He received his Bachelor of Arts degree from New York University in 1886 and his Medical Degree from the New York Homeopathic Medical College and Flower Hospital in 1890. He was long active in the medical profession of New Jersey, serving as a member of the medical staff of Fitkin Memorial Hospital, in Neptune, and as a member and president of the New Jersey State Board of Medical Examiners. He was also a member of the American Institute of Homeopathy and a former president of the New Jersey State Homeopathic Society.

Dr. Bryan had been a Fellow of the American College of Physicians since 1931.

DR. IRVIN REGINALD FOX

Dr. Irvin Reginald Fox was born January 25, 1891, in Oregon City, Ore., and died September 21, 1948, at his home in Eugene, Ore.

Dr. Fox received his M.D. degree from the University of Oregon Medical School in 1921, and, following this, served an internship at Emanuel Hospital in Portland. He entered practice in Eugene and early limited his practice to internal medicine. He soon became a leader in medicine in that city and, at the time of his death, was recognized widely for his ability, his scientific interest, his energy and enthusiasm for the advancement of medicine. This, coupled with his great sincerity, endeared him to his patients and earned for him the respect of his colleagues throughout the state. He was the author of a number of medical articles and was frequent in his attendance at the meetings of the many societies to which he belonged.

During his active career, he was long a member of the Eugene City Board of Health and the Oregon State Board of Medical Examiners. While a member of the staffs of the Eugene and Sacred Heart Hospitals, he worked consistently for the improvement of the standards of medical care in these institutions, and at the time of his death was a member of the governing board of the Sacred Heart Hospital. His influence was important in the development of the high standards at the hospitals where he worked. He was instrumental in organizing a Journal Club which continues to be very active at the present.

Dr. Fox was a fellow of the American Medical Association and of the American College of Chest Physicians, a member of the Oregon State Medical Society, the American Diabetic Society and the North Pacific Society of Internal Medicine. He became a Fellow of the American College of Physicians in 1941.

He enjoyed a very active and extensive practice in his community. The community, his patients and his host of medical friends throughout the Northwest mourn his untimely death and all realize they have lost a great and good friend and doctor.

HOWARD P. LEWIS, M.D., F.A.C.P.,
Governor for Oregon

PROGRAM

THE AMERICAN COLLEGE OF PHYSICIANS

Thirtieth Annual Session

NEW YORK, N. Y.

March 28–April 1, 1949

GENERAL SESSIONS AND LECTURES

Walter W. Palmer, New York, N. Y., President

GENERAL CHAIRMAN

Franklin M. Hanger, New York, N. Y.

COMMITTEE ON ARRANGEMENTS

Franklin M. Hanger, Chairman

Ralph H. Boots
Alexander B. Gutman
Carl Muschenheim
Howard A. Rusk
Theodore B. Russell
Harold J. Stewart
Mrs. Edgar Stillman

COMMITTEE ON AUDITORIUM

Theodore B. Russell, Chairman

Henry Horn
Albert C. Santy
Frank E. Smith, Jr.
Terence Lloyd Tyson
Byard Williams

COMMITTEE ON CLINICS

Harold J. Stewart, Chairman

David P. Barr, New York Hospital
J. Hamilton Crawford, Long Island College Hospital
Clarence E. de la Chapelle, Lenox Hill Hospital
William Dock, Kings County Hospital
Waldo B. Farnum, St. Luke's Hospital
Alexander B. Gutman, Goldwater Memorial Hospital, First Division (Columbia University)
Louis Leiter, Montefiore Hospital for Chronic Diseases
Leo Loewe, Jewish Hospital, Brooklyn
Walter G. Lough, New York University-Bellevue Medical Center, Post-Graduate Medical School and University Hospital
Edwin P. Maynard, Jr., Brooklyn Hospital
Thomas H. McGavack, Flower and Fifth Avenue Hospitals
Rulon W. Rawson, Memorial Hospital
Dickinson W. Richards, Jr., Bellevue Hospital, First (Columbia) Medical Division
Thomas M. Rivers, Hospital of the Rockefeller Institute for Medical Research

Howard F. Shattuck, Roosevelt Hospital
J. James Smith, Bellevue Hospital, Second (Cornell) Medical Division
Isidore Snapper, Mount Sinai Hospital
J. Murray Steele, Goldwater Memorial Hospital, Third Division (New York University)
Bernard Straus, Veterans Administration Hospital, Bronx
William S. Tillett, Bellevue Hospital, Third (New York University) Medical Division
Randolph West, Presbyterian Hospital

COMMITTEE ON ENTERTAINMENT

Ralph H. Boots, Chairman

George C. Andrews, Jr.
Norton S. Brown
Russell L. Cecil
John Staige Davis, Jr.
Richard H. Freyberg
Oswald R. Jones
Bernard S. Oppenheimer
Frank H. Peters
Howard F. Shattuck
Edgar Stillman
Irving S. Wright

COMMITTEE ON HOTELS AND TRANSPORTATION

Carl Muschenheim, Chairman

Gurney Taylor
David Ulmar

COMMITTEE ON PANEL DISCUSSIONS

Alexander B. Gutman, Chairman

John H. Keating
Henry G. Kunkel
Louis Leiter
Edward C. Reifenstein, Jr.
Ephraim Shorr
Louis J. Soffer
J. Murray Steele
Bernard Straus

COMMITTEE ON PUBLICITY

Howard A. Rusk, Chairman

Arthur J. Antenucci
Frederick R. Bailey
Howard G. Bruenn
Charles K. Friedberg

COMMITTEE ON TECHNICAL EXHIBITS

George Morris Piersol, Chairman

Thomas Klein
Charles C. Wolferth

COMMITTEE ON WOMEN'S ENTERTAINMENT

Mrs. Edgar Stillman, Chairman

Mrs. George Baehr
Mrs. Alvan L. Barach
Mrs. Louis F. Bishop, Jr.
Mrs. Ralph H. Boots
Mrs. Russell L. Cecil
Mrs. Henry T. Chickering
Mrs. G. Jarvis Coffin
Mrs. Jean A. Curran, Sr.
Mrs. A. L. Garbat
Mrs. Franklin M. Hanger
Mrs. Albert R. Lamb, Sr.
Mrs. Robert L. Levy

Mrs. Edwin P. Maynard, Jr.
Mrs. Currier McEwen
Mrs. James Alexander Miller
Mrs. Walter W. Palmer
Mrs. Harold E. B. Pardee
Mrs. Cornelius P. Rhoads
Mrs. Thomas M. Rivers
Mrs. Howard F. Shattuck
Mrs. Frank E. Smith, Jr.
Mrs. Louis J. Soffer
Mrs. Gurney Taylor
Mrs. Kenneth Taylor

INVITATION

As one of the world's greatest medical centers, New York extends its welcome to the Fellows, Associates and friends of The American College of Physicians. Those that reside in the Greater New York area, the New York Academy of Medicine, the County Medical Societies, the local hospitals and medical centers and the Department of Health of the City of New York, are anxious that your visit to New York be not only as professionally profitable but as comfortable and entertaining as possible. Since the College was last our guest ten years ago, there have been many changes in our city. New and great medical institutions and services such as the Public Health Research Institute, the Sloan-Kettering Institute for Cancer Research, the Montefiore and Department of Hospitals' home care programs, the United Medical Service and Health Insurance Plan of New York, the New York University-Bellevue Medical Center, the Hospital Council of Greater New York have been started. Our other internationally known hospitals, clinics, foundations and services, and our five medical schools—Columbia University College of Physicians and Surgeons, New York University College of Medicine, Cornell University Medical College, Long Island College of Medicine and New York Medical College, Flower and Fifth Avenue Hospitals—have continued their leadership. They too are anxious that you have every opportunity while in New York to share their advances with them.

Our New York Academy of Medicine, which observed its centennial last year, invites you to visit its building at 2 E. 103rd Street and to make use, if you desire, of its medical library, the second largest collection of medical literature in the United States. Center for the activities of practicing physicians and surgeons of New York, the Academy of Medicine is headquarters for many local and national medical groups.

As New York is also one of the world's greatest centers of culture, entertainment, commerce and industry, we welcome you to those aspects of New York and bid you share in that which may not be available in your own community. The shops along Fifth Avenue, Times Square at night, the view from the Empire State Building, the Metropolitan Museum of Art, Rockefeller Foundation, the intimate restaurants serving foreign foods, Chinatown, the big brassy night clubs, the American Museum of Natural History, the theaters and the opera, the oratory at Union Square, the carriage rides in Central Park, The Little Church Around the Corner, the craft shops in Greenwich Village—these are ours, they are the things that make New York, the New York of O. Henry, Mark Hellinger, and Damon Runyon. This week of our Meeting, they are yours also. We hope you enjoy them as much as we.

FATHER KNICKERBOCKER

GENERAL INFORMATION

GENERAL HEADQUARTERS

Waldorf-Astoria Hotel

Park Avenue and 50th Street

Registration headquarters, the information bureau, technical exhibits, general sessions, morning lectures, panel discussions, certain selected clinics and clinico-patho-

logical conferences, meetings of committees, of the Board of Regents, and of the Board of Governors. The Annual Convocation and the Annual Banquet will take place in the Grand Ballroom of this Hotel.

HOTEL ACCOMMODATIONS

A fully adequate number of first-class guest rooms has been reserved in close proximity to the Waldorf-Astoria Hotel, and a Housing Bureau, working through the Committee on Hotels and Transportation, has been set up at the New York Convention Bureau, 500 Park Avenue, New York 22, N. Y. Applications for rooms should be made to this Bureau, preferably on the official form provided by the College, but in the absence of the form, the Housing Bureau will handle letters of application, provided the applicant identifies himself with the College and its Annual Session. It is requested that five choices of hotels be indicated, and that a reasonable range of rates be shown. Whenever possible arrangements should be made for occupancy of rooms accommodating two persons. Confirmation from the hotel where the reservation has been made will be mailed to each applicant. If, after making reservations, the applicant finds it impossible to attend, he is requested to notify the Housing Bureau promptly so that his accommodations may be made available to another physician.

A very limited number of rooms were made available at the Waldorf-Astoria Hotel, but adequate and satisfactory accommodations are available nearby.

LIST OF OFFICIAL HOTELS

Hotel	Type of Room and Rate*	
WALDORF-ASTORIA	100 doubles	$10.00 to $16.00
Park Avenue and 50th Street	25 suites	18.00 to 32.00
BELMONT-PLAZA	90 doubles	$ 6.50 to $ 9.50
Lexington Avenue and 49th Street	5 suites	12.00 to 15.00
ABBEY	12 singles	$ 3.75 to $ 5.00
149 W. 51st Street	38 doubles	6.00 to 8.00
AMBASSADOR	10 doubles	$ 9.00 to $14.00
Park Avenue and 51st Street	5 suites	16.00 to 25.00
BARCLAY	50 doubles	$11.00 to $13.00
111 E. 48th Street		
BILTMORE	100 doubles	$10.00 to $17.00
Madison Avenue and 43d Street		
COMMODORE	70 singles or doubles	
Lexington Avenue and 42nd Street	singles	$ 5.50 to $ 7.50
	doubles	8.50 to 10.00
	200 twins	11.50
	15 combinations	13.00
DELMONICO	6 singles	$10.00
502 Park Avenue	10 suites	18.00 to $22.00
GOTHAM	10 doubles	$ 9.00 to $14.00
Fifth Avenue and 55th Street		
NEW WESTON	30 doubles	$ 8.00 to $10.00
34 E. 50th Street	5 suites	12.00 to 20.00
PARK CENTRAL	50 doubles	$ 8.50 to $10.00
Seventh Avenue and 56th Street	75 suites	10.00 to 14.00
PICCADILLY	75 doubles	$ 6.00 to $ 8.00
227 W. 45th Street		

PLAZA	10 singles	$ 9.00 to $12.00
Fifth Avenue and 59th Street	40 doubles	10.00 to 18.00
ROOSEVELT	50 singles	$ 6.50 to $10.00
Madison Avenue and 45th Street	350 doubles	10.50 to 15.00
ST. REGIS	3 singles	$ 8.00 to $10.00
Fifth Avenue and 55th Street	6 doubles	12.00 to 14.75
SHELTON	25 singles	$ 4.50 to $ 6.50
Lexington Avenue and 49th Street	75 doubles	6.50 to 8.00
SHERATON	10 doubles	$ 8.00 to $10.00
303 Lexington Avenue	10 suites	10.00 to 12.50
TAFT	50 singles	$ 4.00 to $ 7.00
Seventh Avenue and 50th Street	150 doubles	6.50 to 9.00
VANDERBILT (10 minutes by cab)	10 singles	$ 4.50 to $ 7.00
Park Avenue and 34th Street	15 doubles	8.00 to 10.00
VICTORIA	10 singles	$ 5.00
Seventh Avenue and 51st Street	65 doubles	7.00 to $ 9.00
WARWICK	75 doubles	$12.00
65 W. 54th Street	25 suites	20.00
WENTWORTH	20 doubles	$ 7.00 to $ 8.00
59 W. 46th Street	15 suites	12.00 to 14.00
WINTHROP	6 doubles	$ 7.00 to $ 9.00
Lexington Avenue and 47th Street		

* Subject to 5 per cent New York City Sales Tax.

Who May Register—

(*a*) All members of The American College of Physicians in good standing for 1949.

(*b*) All newly elected members.

(*c*) Graduate medical students pursuing courses at medical schools in Greater New York, without registration fee, **upon presentation of matriculation cards or other evidence of registration at these institutions;** admission to exhibits, general sessions and morning lectures.

(*d*) Members of the staff, including interns, of the hospitals participating in the program, without registration fee, **upon presentation of proper identification;** admission to exhibits, general sessions and morning lectures.

(*e*) Members of the Medical Corps of the Army, Navy, Public Health Service and Veterans Administration, either of the United States or Canada, without registration fee, **upon presentation of proper credentials.**

(*f*) Qualified physicians who may wish to attend this Session as visitors or in company with physicians who are members of the College; such physicians shall pay a registration fee of $15.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

Registration Bureau—While official registration will start on Monday morning, March 28, advance registration of members and exhibitors will be provided for on Sunday, March 27, from 2:30 to 5:00 in the afternoon. The Registration Bureau, located in the Silver Corridor, Ballroom Floor, will be open through the week from 8:30 A.M. to 5:45 P.M.

Registration Blanks for all Clinics, Clinico-Pathological Conferences and Panel Discussions will be sent with the individual program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Board for special announcements will be located near the Registration Bureau at the Waldorf-Astoria.

Transportation—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the Meeting.

The General Business Meeting of the College will be held from 2:00 to 2:40 P.M., Thursday, March 31, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the annual reports of the Secretary-General, Executive Secretary and Treasurer, and the presentation of certain amendments to the Constitution and By-Laws. The President-Elect, Dr. Reginald Fitz, Boston, Mass., will be inducted into office.

Board and Committee Meetings—All meetings will be held at the Waldorf-Astoria. Special meetings will be announced and posted.

A Dinner Meeting of the Board of Regents and of the Board of Governors will be held in the Jansen Suite, Fourth Floor of the Waldorf-Astoria, Sunday, March 27, at 7:00 P.M.

Committee on Credentials

Saturday, March 26, 10:00 A.M., Carpenter Salon, Fourth Floor

Committee on Credentials and Executive Committee

Saturday, March 26, 2:30 P.M., Carpenter Salon, Fourth Floor

Committee on Fellowships and Awards

Sunday, March 27, 10:00 A.M., Carpenter Salon, Fourth Floor

Committee on Educational Policy and Advisory Committee on Postgraduate Courses

Sunday, March 27, 11:00 A.M., Carpenter Salon, Fourth Floor

Joint Meeting: Board of Regents and Board of Governors

Sunday, March 27, 2:00 P.M., Jansen Suite, Fourth Floor

Committee on Nominations

Monday, March 28, 10:00 A.M., Carpenter Suite, Fourth Floor

Committee on Finance

Monday, March 28, 10:00 A.M., Chinese Room, Fourth Floor

Committee on Public Relations

Monday, March 28, 11:00 A.M., Carpenter Salon, Fourth Floor

Board of Regents

Tuesday, March 29, 12:00 M., Carpenter Salon, Fourth Floor *
Friday, April 1, 12:00 M., Carpenter Salon, Fourth Floor *

Board of Governors

Wednesday, March 30, 12:00 M., Carpenter Salon, Fourth Floor *

SPECIAL FEATURES

Special Trains—No official arrangements have been concluded for complete special trains, but, in numerous localities in the West and Far West, the College Governors have sponsored special cars on certain trains to New York and return. Members are advised to consult the Governors for their states on provisions concerning special cars.

Post-Convention Cruise to Bermuda—A special post-convention cruise to Bermuda has been arranged at the request of members and their families and friends. The cruise will be under the direction of Mr. Leon V. Arnold, Travel Consultant, 36 Washington Square West, New York 11, N. Y. The number of accommodations is somewhat limited and members are urged to communicate immediately with Mr. Arnold to secure plans of the ship, to select staterooms and to complete reservations.

The Queen of Bermuda will leave New York City at 3:00 P.M., Monday, April 4, arriving at Hamilton, Bermuda, 7:00 A.M., April 6. Guests will be accommodated at the Hotel Bermudiana and at the Hotel Princess. Motor or carriage drives to St. George's, Somerset, Gibb's Hill or Spanish Point will be arranged; time available to visit the celebrated caves and coral underseas gardens; to shop; golf; to follow the camera or other diversions. Party will cast off from Hamilton at 3:00 P.M., April 8, arriving back in New York at 9:00 A.M., April 10.

Grand Reception, March 28, 5:00 to 7:00 P.M.—The combined men's and women's Committees on Entertainment have arranged a Grand Reception and Cocktail Party on Monday evening, 5:00 to 7:00 P.M., in the Starlight Roof of the Waldorf-Astoria. This will be a feature of the entertainment program, an opportunity for all in attendance to assemble for an hour or two of sociability and for renewing acquaintanceships and seeing "Who's Here." Tickets available at the Registration Bureau in the Silver Corridor and at the Women's Registration Headquarters, Fourth Floor of the Waldorf-Astoria. Price, $3.00.

The Annual Convocation and the President's Reception, Wednesday, March 30—The Annual Convocation of the College will be held at 8:30 P.M., March 30, in the Grand Ballroom of the Waldorf-Astoria. All members of the College and their families, and those of the public who are interested, are cordially invited. All physicians elected Fellows of the College since the 1948 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors and new Fellows to be inducted are requested to assemble in Le Perroquet Suite, Fourth Floor, at 7:45 P.M., preparatory to the formation of the procession. They will be conducted to their seats by the Marshal of the Convocation, Dr. T. Grier Miller, promptly at 8:30 o'clock. It is suggested that all appear in evening clothes.

The Convocation ceremony will include the President's address and a Convocational Oration by Henry Allen Moe, Secretary General, The John Simon Guggenheim Memorial Foundation, New York, N. Y. The John Phillips Memorial Medal for 1949, the James D. Bruce Memorial Medal for 1949 and the Alfred Stengel Diploma for 1949 will be awarded. Recipients of Research Fellowships of the College for 1949 will be announced, and Masterships will be conferred upon four outstanding Fellows of the College. The new Fellows to be inducted will be presented by the Secretary General, Dr. George Morris Piersol, and, after subscribing to the Fellowship Pledge, will be inducted by the President. Following the Convocation, after a brief inter-

* Buffet Luncheon served.

mission during which guests will retire to the Foyer while the Ballroom is cleared, the President's Reception and Dance will take place in the Ballroom. All members and guests are requested to pass along the receiving line at the Reception.

The Annual Banquet—A "Dutch Treat" Cocktail Party has been arranged from 7:00 to 8:00 P.M. in the Sert Room, Office Floor, of the Waldorf-Astoria Hotel. All are encouraged to joint in this general preprandium instead of having numerous and scattered private parties. The Annual Banquet will be held in the Grand Ballroom of the Waldorf-Astoria at 8:00 P.M., Thursday, March 31. Some unusual musical features are planned and the speaker will be an individual of national or international reputation whose name and title will be announced later. The Annual Banquet should be a sparkling and delightful occasion at which every member, his guests and friends should be present. Table reservations for groups may be arranged. Tickets should be obtained at the Registration Bureau by Wednesday afternoon, March 30, so that adequate preparations can be consummated.

Other General Entertainment Features

Monday Night Theater Parties, March 28—The Entertainment Committee will publish a list of the plays appearing at that time, with prices, and arrangements have been made whereby members of the College may apply for tickets in advance to Sullivan's Theater Ticket Office, Waldorf-Astoria Hotel. A service charge of $.75 for each ticket will be made by the agency. It is suggested that members indicate first, second and third choice of plays.

Radio City Music Hall, Tuesday, March 29—Nine hundred and forty-four reserved seats are available in the Mezzanine. The stage show starts about 9:00 P.M. Ticket holders should arrive between 8:30 P.M. and 9:00 P.M. Price of seats, $2.40.

Entertainment of Visiting Women—The Women's Entertainment Committee has prepared the following program to welcome to New York the wives of the members of the American College of Physicians, hoping that they will enjoy their visit and take away with them pleasant memories of their stay. Those arriving early may register Sunday afternoon, March 27, from 2:30 to 5:00 P.M. in the Assembly Suite on the Fourth Floor of the Waldorf-Astoria. Registration will continue Monday through Thursday from 9:00 A.M. to 4:00 P.M.

Certain of the entertainment features are limited in accommodations and, therefore, early registration for each event is essential.

Monday, March 28, 1949

9:00 A.M. to 4:00 P.M., Registration, Room 4M, Assembly Suite, Fourth Floor, Waldorf-Astoria.

5:00 P.M. to 7:00 P.M., Grand Reception and Cocktail Party for members and their wives, Starlight Roof. Tickets, $3.00.

Evening: Free.

Tuesday, March 29, 1949

Morning: 10:00 A.M. Trip to United Nations, Lake Success. Tour, $2.00.

Afternoon: 2:00 P.M. to 4:00 P.M. Tour of downtown Manhattan. Buses leave from and return to 49th Street entrance, Waldorf-Astoria. $2.00.

Trips to the Planetarium, Good Housekeeping Institute (model kitchens, laundries, beauty clinics, etc.), New York Telephone Company and various broadcasts have also been arranged. Information and tickets will be available at the Women's Registration Desk.

4:30 P.M. to 6:30 P.M. Reception Tea in the Cosmopolitan Club, 129 E. 65th Street, as guests of the Women's Committee.

Evening: 9:00 P.M. Reserved seats for regular performance at Radio City Music Hall. Tickets, $2.40.

Wednesday, March 30, 1949

Morning: Free.

Afternoon: 12:30 P.M. to 2:30 P.M. Luncheon and "Suddenly It's Spring" Fashion Show, arranged by Lord and Taylor. Starlight Roof, Waldorf-Astoria. Tickets, $5.00.

Evening: 8:30 P.M. Convocation, followed by President's Reception and Dance, Ballroom, Waldorf-Astoria.

Thursday, March 31, 1949

Morning: 10:00 A.M. Trip to the United Nations, Lake Success. Guests may return before or after luncheon in the United Nations cafeteria. Tour, $2.00.

As on Tuesday, trips to the Good Housekeeping Institute, New York Telephone Company and various broadcasts have been arranged. Information and tickets will be available at the Women's Registration Desk in Room 4M, Assembly Suite, Waldorf-Astoria.

Afternoon: Free.

Evening: 7:00 P.M. to 8:00 P.M. "Dutch Treat" Cocktail Party, Sert Room, Waldorf-Astoria. 8:00 P.M. Annual Banquet of the College, Ballroom, Waldorf-Astoria.

Lists of restaurants, shops, beauty parlors, moving picture houses and theaters will be available, specially prepared by the Women's Committee for the use of the College guests. The Committee will also be glad to provide suggestions and information for individual trips to such places of interest as antique shops, art galleries, auction rooms, churches, Empire State Building Observatory, French Lines, historical landmarks, Macy's behind-the-scenes, museums, Waldorf behind-the-scenes, zoos and botanical gardens.

For the Children—Trips to the zoo, CBS children's programs, Museum of Science and Industry, Museum of the City of New York, etc., can be arranged. Chaperones and sitters available through the Registration Committee at $1.00 an hour.

A Women's Reservation Card will accompany the formal program of the Annual Session to be distributed to every member of the College. It is urgently requested that the men see that these cards are promptly handed to their wives so that tentative reservations may be made early by mail.

SPECIAL PROGRAM

SILVER HILL FOUNDATION FOR THE TREATMENT OF THE PSYCHONEUROSES

New Canaan, Conn.

Saturday, April 2, 1949, 10:30 A.M.–12:30 P.M.

New Canaan is forty miles from New York. Seventy-five members are cordially invited to attend as guests of the Foundation. Buses will leave the Waldorf-Astoria

at 9:00 A.M. The Clinic will be from 10:30 A.M. to 12:30 P.M.; luncheon at 1:00 P.M.. Buses will depart for return to New York at 2:30 P.M.

PROGRAM

Auditorium

(Capacity, 75)

William B. Terhune, presiding

Lecture Clinic on Brief, Intensive, Flexible Methods of Psychotherapy

1. Basic Principles of Brief, Practical Psychotherapy.
   William B. Terhune.
2. Description of Reëducational Methods and Applicability.
   Franklin S. DuBois.
3. Presentation of Case History and Discussion of Practical Methods of Treatment.
   Robert B. Hiden.

THE TECHNICAL EXHIBIT

The Technical Exhibit will be located on the Ballroom Floor of the Waldorf-Astoria and will practically surround the Ballroom, since it will be conducted in all of the adjoining halls on that floor. The Committee on Exhibits of the College maintains highest possible standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation; irrelevant products are eliminated, and only firms which present a group of approved products of scientific interest to the internist and allied specialists may exhibit.

The exhibitor's aim is to announce new products and to present new and interesting information to members and guests of the College. Likewise, many exhibitors take advantage of this opportunity to give aid and service directions to members who have previously purchased their products. Furthermore, this Exhibit provides the only convenient and direct method of contacting, personally, members of the College.

Members and guests of the College are encouraged to accord the exhibitors courteous and interested attention, thus recognizing their contributions to the Meeting and the effort that they make and the expense to which they go in building superior displays and furnishing, freely, valuable information.

The Exhibits will be open from 8:30 A.M. to 5:45 P.M. daily from Monday through Thursday, and from 8:30 A.M. to 2:45 P.M. on Friday. Special intermissions will be arranged, providing additional time for the inspection of exhibits.

1949 EXHIBITORS

Abbott Laboratories, North Chicago, Ill.
American Hospital Supply Corporation, Evanston, Ill.
Ames Company, Inc., Elkhart, Ind.
Appleton-Century-Crofts, Inc., New York, N. Y.
Armour Laboratories, The, Chicago, Ill.
Association of American University Presses
Ayerst, McKenna & Harrison, Limited, New York, N. Y.

Baum Co., Inc., W. A. New York, N. Y.
Becton, Dickinson & Co., Rutherford, N. J.
Bilhuber-Knoll Corp., Orange, N. J.
Blakiston Company, The, Philadelphia, Pa.
Bristol Laboratories, Inc., Syracuse, N. Y.
Burdick Corporation, The, Milton, Wis.
Burroughs Wellcome & Co. (U. S. A.) Inc., Tuckahoe, N. Y.
Burton Manufacturing Company, Chicago, Ill.

Cambridge Instrument Co., Inc., New York, N. Y.
Cameron Surgical Specialty Company, Chicago, Ill., and New York, N. Y.
Carnation Company, Los Angeles, Calif.
Ciba Pharmaceutical Products, Inc., Summit, N. J.
Collins, Inc., Warren E., Boston, Mass.
Commercial Solvents Corporation, New York, N. Y.
Coreco Research Corporation, New York, N. Y.
Cream of Wheat Corporation, The, Minneapolis, Minn.

Davies, Rose & Company, Limited, Boston, Mass.
Davis Company, F. A., Philadelphia, Pa.
Denver Chemical Mfg. Co., Inc., The, New York, N. Y.
Devereux Schools, Devon, Pa., and Santa Barbara, Calif.
Dietene Company, The, Minneapolis, Minn.
Doak Company, Inc., Cleveland, Ohio
Doho Chemical Corporation, The, New York, N. Y.

E & J Manufacturing Company, Glendale, Calif.
Edgerly, Patricia, The New York Medical Exchange
Electro-Physical Laboratories, Inc., New York, N. Y.

Fleet Co., Inc., C. B., Lynchburg, Va.
Flint, Eaton & Company, Decatur, Ill.

General Electric X-Ray Corporation, Milwaukee, Wis.
Gerber Products Company, Fremont, Mich.
Gradwohl Laboratories, St. Louis, Mo.
Grune & Stratton, Inc., New York, N. Y.

Harrower Laboratory, Inc., The, Glendale, Calif.
Heinz Company, H. J., Pittsburgh, Pa.
Hoeber, Inc., Paul B., New York, N. Y.
Hoffmann-La Roche, Inc., Nutley, N. J.
Hollister-Stier Laboratories, Spokane, Wash., Wilkinsburg, Pa., and Los Angeles, Calif.
Horn Company, William S., Fort Worth, Tex.

International Vitamin Division, Ives-Cameron Company, Inc., New York, N. Y.
Iodine Educational Bureau, Inc., New York, N. Y.

Jones Metabolism Equipment Co., Chicago, Ill.
"Junket" Brand Foods, Division of Chr. Hansen's Laboratory, Little Falls, N. Y.

Kalak Water Co. of New York, Inc., New York, N. Y.
Kelley-Koett Manufacturing Co., The, Covington, Ky.
Kellogg Company, Battle Creek, Mich.
Knox Gelatine Co., Inc., Chas. B., Johnstown, N. Y.

LaMotte Chemical Products Company, Baltimore, Md.
Larson, Burneice, The Medical Bureau, Chicago, Ill.
Lea & Febiger, Philadelphia, Pa.
Lederle Laboratories Division, American Cyanamid Company, New York, N. Y.
Lilly and Company, Eli, Indianapolis, Ind.
Lippincott Company, J. B., Philadelphia, Pa.

Macmillan Company, The, New York, N. Y.
Maltine Company, The, Morris Plains, N. J.
McNeil Laboratories, Inc., Philadelphia, Pa.
Mead Johnson & Company, Evansville, Ind.
Medical Bureau, The, Chicago, Ill.
Medical Case History Bureau, New York, N. Y.
Medical Film Guild, New York, N. Y.
Merck & Co., Inc., Rahway, N. J.
Merrell Company, The Wm. S., Cincinnati, Ohio
Mosby Company, The C. V., St. Louis, Mo.

Nelson & Sons, Thomas, New York, N. Y.
New York Medical Exchange, The, New York, N. Y.

Oxford University Press, Inc., New York, N. Y.

Parke, Davis & Company, Detroit, Mich.
Patch Company, The E. L., Boston, Mass.
Picker X-Ray Corporation, New York, N. Y.
Procter & Gamble Company, The, Cincinnati, Ohio

Reed & Carnrick, Jersey City, N. J.

Sanborn Company, Cambridge, Mass.
Sandoz Chemical Works, Inc., New York, N. Y.
Saunders Company, W. B., Philadelphia, Pa.
Schenley Laboratories, Inc., New York, N. Y.
Schering Corporation, Bloomfield, N. J.
Sharp & Dohme, Inc., Philadelphia, Pa.
Smith, Kline & French Laboratories, Philadelphia, Pa.
Squibb & Sons, E. R., New York, N. Y.

Technicon Cardiograph Corp., New York, N. Y.

U. M. A. Inc., New York, N. Y.
Upjohn Company, The, Kalamazoo, Mich.
U. S. Vitamin Corporation, New York, N. Y.

Varick Pharmacal Co., Inc., New York, N. Y.

Wallace & Tiernan Products, Inc., Belleville, N. J.
Warren-Teed Products Company, The, Columbus, Ohio
Westwood Pharmaceuticals, Division of Foster-Milburn Company, Buffalo, N. Y.
White Laboratories, Inc., Newark, N. J.
Williams & Wilkins Company, The, Baltimore, Md.
Winthrop-Stearns Inc., New York, N. Y.
Woodward Medical Personnel Bureau, Chicago, Ill.
Wyeth Incorporated, Philadelphia, Pa.

Year Book Publishers, Inc., The, Chicago, Ill.

GENERAL OUTLINE OF NEW YORK SESSION

Hotel events are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	March 28	**March 29**	**March 30**	**March 31**	**April 1**
9:15 A.M. to 11:30 A.M.	Morning free. **Registration, Exhibits, etc.**	Hospital Clinics*	**Morning Lectures†** (9:30–11:30)	Hospital Clinics*	**Morning Lectures†** (9:30–11:30)
12:00 M. to 1:15 P.M.		**Panel Discussions**	**Panel Discussions**	**Panel Discussions**	**Panel Discussions**
1:15 P.M. to 2:00 P.M.	**Luncheon**	**Luncheon**	**Luncheon**	**Luncheon**	**Luncheon**
2:00 P.M. to 5:00 P.M.	**1st General Session**	**2nd General Session**	**3rd General Session**	**Annual Business Meeting 4th General Session**	**5th General Session**
5:00 P.M. to 7:00 P.M.	**Grand Reception (Starlight Roof)**				
8:00 P.M. to 11:00 P.M.			**Convocation, Followed By President's Reception**	**Annual Banquet**	

* A few clinics and clinical-pathological conferences will be held in the hotel.
† Two simultaneous series.
Note: Exhibits will be open Monday through Thursday from 8:30 A.M. to 5:45 P.M.; on Friday, from 8:30 A.M. to 2:45 P.M.

GENERAL SESSIONS PROGRAM

Grand Ballroom, Waldorf-Astoria Hotel

FIRST GENERAL SESSION

Monday Afternoon, March 28, 1949

General Chairman, Franklin M. Hanger, F.A.C.P., presiding

P.M.

2:00 Addresses of Welcome:

The Honorable WILLIAM O'DWYER, Mayor of New York City.

WILLARD C. RAPPLEYE, F.A.C.P., Dean, Columbia University College of Physicians and Surgeons.

WILLIAM B. RAWLS, F.A.C.P., President, New York County Medical Society.

LEO F. SIMPSON, F.A.C.S., President, The Medical Society of the State of New York.

BENJAMIN P. WATSON, F.R.C.S., F.A.C.S., President, New York Academy of Medicine.

Response to Addresses of Welcome:

WALTER W. PALMER, F.A.C.P., President, The American College of Physicians.

President Walter W. Palmer, F.A.C.P., presiding

2:30 The James D. Bruce Lecture on Preventive Medicine: The Hospital as a Center of Preventive Medicine.

STANHOPE BAYNE-JONES (by invitation), President of the Joint Administrative Board, The New York Hospital-Cornell College Association, New York, N. Y.

3:15 INTERMISSION.

3:35 The Diagnosis and Management of Atypical or Virus Pneumonia.

JOHN H. DINGLE (by invitation), Elizabeth Severance Prentiss Professor of Preventive Medicine, and Associate Professor of Medicine, Western Reserve University School of Medicine, Cleveland, Ohio.

3:55 Immunologic Types of Blastomycosis.

DAVID T. SMITH, F.A.C.P., Professor of Bacteriology and Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C.

4:15 Treatment of Syphilis.

J. EARLE MOORE (by invitation), Associate Professor of Medicine, Johns Hopkins University School of Medicine; Adjunct Professor of Public Health Administration, Johns Hopkins University School of Hygiene and Public Health; Baltimore, Md.

4:35 Prefrontal Operations for the Treatment of Mental Illnesses.

J. LAWRENCE POOL (by invitation), Professor of Neurological Surgery, Columbia University College of Physicians and Surgeons; Director of the Service of Neurological Surgery, Neurological Institute; New York, N. Y.

4:55 ADJOURNMENT.

SECOND GENERAL SESSION

Grand Ballroom, Waldorf-Astoria Hotel

Tuesday Afternoon, March 29, 1949

Presiding Officer
Reginald Fitz, F.A.C.P., Boston, Mass.

P.M.

2:00 **Dietary Invalidism.**
HENRY J. JOHN, F.A.C.P., Physician, Lakeside and St. Luke's Hospitals, Cleveland, Ohio.

2:50 **Researches in Coronary Heart Diseases.**
PAUL D. WHITE, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital; Boston, Mass.

3:10 **Lower Nephron Nephrosis.**
WILLIAM GOLDRING, F.A.C.P., Associate Professor of Medicine, New York University College of Medicine; Visiting Physician, Bellevue Hospital; New York, N. Y.

3:30 INTERMISSION.

3:50 **Clinical Significance of Cryoglobulinemia.**
DAVID P. BARR, F.A.C.P., Professor of Medicine, Cornell University Medical College; Physician-in-Chief, New York Hospital; New York, N. Y.

4:10 **Clinical Angiocardiography.**
ISRAEL STEINBERG, F.A.C.P., Instructor in Radiology and Medicine, Cornell University Medical College; Assistant Radiologist, New York Hospital; New York, N. Y.
CHARLES T. DOTTER (by invitation), Instructor in Medicine, Cornell University Medical College; Resident in Radiology, New York Hospital; New York, N. Y.

4:30 **Diagnosis and Treatment of Pheochromocytoma.**
GEORGE F. CAHILL, F.A.C.S. (by invitation), Professor of Urology, Columbia University College of Physicians and Surgeons; Director, Squier Urological Service, Presbyterian Hospital; New York, N. Y.

4:50 ADJOURNMENT.

THIRD GENERAL SESSION

Grand Ballroom, Waldorf-Astoria Hotel

Wednesday Afternoon, March 30, 1949

Presiding Officer
LeRoy H. Sloan, F.A.C.P., Chicago, Ill.

P.M.

2:00 **The John Phillips Memorial Lecture: The Natural Occurrence of Antithyroid Compounds as a Cause of Simple Goiter.**
EDWIN B. ASTWOOD, F.A.C.P., Research Professor of Medicine, Tufts College Medical School; Endocrinologist, Joseph H. Pratt Diagnostic Hospital; Physician, The Boston Dispensary; Boston, Mass.

2:45 **Therapeutic Possibilities of Para-Aminobenzoic Acid.**
C. J. D. ZARAFONETIS (by invitation), Assistant Professor and Research Associate in the Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

3:05 INTERMISSION.

3:25 **Electron Microscopy in Relation to the Medical Sciences.**
STUART MUDD (by invitation), Professor of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia, Pa.

3:45 **Present Status of Aureomycin Therapy.**
MAXWELL FINLAND, F.A.C.P., Associate Professor of Medicine, Harvard Medical School; Associate Physician, Thorndike Memorial Laboratory, and Chief, Fourth Medical Service, Boston City Hospital; Boston, Mass.

4:05 **Chloromycetin and Aureomycin: Therapeutic Results.**
THEODORE E. WOODWARD (by invitation), Associate Professor of Medicine, University of Maryland School of Medicine, Baltimore, Md.

4:25 **Poliomyelitis: Early Diagnosis and Early Management of Acute Cases.**
JOHN R. PAUL, F.A.C.P., Professor of Preventive Medicine, Yale University School of Medicine, New Haven, Conn.

4:45 **The Clinical Features and Laboratory Diagnosis of Rickettsial Pox.**
HARRY M. ROSE (by invitation), Associate Professor of Medicine, Columbia University College of Physicians and Surgeons; Assistant Visiting Physician, Presbyterian Hospital; New York, N. Y.

5:05 ADJOURNMENT.

FOURTH GENERAL SESSION

Grand Ballroom, Waldorf-Astoria Hotel

Thursday Afternoon, March 31, 1949

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary-General, Executive Secretary and the Treasurer; elections of new Officers, Regents and Governors will take place; certain amendments to the Constitution and By-Laws will be presented; President-Elect Reginald Fitz of Boston, Mass., will be inducted as President and will make a brief inaugural address.

Presiding Officer
Charles F. Moffatt, F.A.C.P., Montreal, Can.

2:40 **Emotional Factors in Organic Disease.**
WILLIAM C. MENNINGER, F.A.C.P., Professor of Clinical Psychiatry, University of Kansas School of Medicine; General Secretary, The Menninger Foundation; Topeka, Kans.

3:00 INTERMISSION.

3:20 **The Use of Isotopes as Metabolic Tracers.**
DEWITT STETTEN, JR. (by invitation), Member and Chief of Division of Nutrition and Physiology, The Public Health Research Institute of The City of New York, Inc., New York, N. Y.

3:40 **Therapeutic Considerations in Ulcerative Colitis.**
WALTER L. PALMER, F.A.C.P., Professor of Medicine, University of Chicago School of Medicine, Chicago, Ill.

4:10 **Surgery of the Malignant Tumors of the Ampullary Area and Pancreas.**
ALLEN O. WHIPPLE, F.A.C.S., Clinical Director of Surgery, Memorial Hospital, New York, N. Y.

4:20 **The Treatment of Bleeding Esophageal Varices by Portacaval Shunts.**
ROBERT R. LINTON, F.A.C.S., Assistant Clinical Professor of Surgery, Harvard Medical School; Chief of the Peripheral Vascular Service and Senior Visiting Surgeon, Massachusetts General Hospital; Boston, Mass.

4:40 **The Use of Mixtures of Protamine Zinc and Regular Insulin.**
RANDALL G. SPRAGUE, F.A.C.P., Assistant Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant, Division of Medicine, Mayo Clinic; Rochester, Minn.

5:00 ADJOURNMENT.

FIFTH GENERAL SESSION

Grand Ballroom, Waldorf-Astoria Hotel

Friday Afternoon, April 1, 1949

Presiding Officer
A. B. Brower, F.A.C.P., Dayton, Ohio

P.M.

2:00 **The Acute Radiation Syndrome in Man.**
SHIELDS WARREN (by invitation), Director, Division of Biology and Medicine, Atomic Energy Commission; Professor of Pathology, Harvard Medical School; Boston, Mass.
JOHN Z. BOWERS (Associate), Deputy Director, Division of Biology and Medicine, Atomic Energy Commission, Washington, D. C.

2:30 **Gouty Arthritis.**
JOHN H. TALBOTT, F.A.C.P., Professor of Medicine, The University of Buffalo School of Medicine; Director of Medical Service, Buffalo General Hospital; Buffalo, N. Y.

2:50 **Migraine and Histaminic Cephalalgia.**
BAYARD T. HORTON, F.A.C.P., Associate Professor of Medicine, University of Minnesota (Mayo Foundation); Consultant in Medicine and Head of Section on Clinical Investigation, Mayo Clinic; Rochester, Minn.

3:20 INTERMISSION.

3:40 **The Etiology of Rheumatic Fever.**
HOMER F. SWIFT (by invitation), Member Emeritus of The Rockefeller Institute for Medical Research, New York, N. Y.

4:00 **Hypersplenism.**
CHARLES A. DOAN, F.A.C.P., Dean, Professor of Medicine and Director of Medical Research, The Ohio State University College of Medicine, Columbus, Ohio.

4:20 **The Treatment of Pernicious Anemia with Vitamin B_{12}.**
RANDOLPH WEST, F.A.C.P., Professor of Medicine, Columbia University College of Physicians and Surgeons; Attending Physician, Presbyterian Hospital; New York, N. Y.

4:40 ADJOURNMENT.

MORNING LECTURES

The Morning Lectures recognize the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures enable the speaker to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

Morning Lectures will be offered on Wednesday and Friday mornings only; Hospital Clinics on Tuesday and Thursday mornings only. Two series of Morning Lectures will be presented concurrently in the Ballroom and Starlight Roof of the Waldorf-Astoria Hotel.

The Lectures will be open to all members and guests of the College.

Admission by regular registration badge; no special tickets.

Wednesday, March 30, 1949

Grand Ballroom, Waldorf-Astoria Hotel

Presiding Officer
William S. Middleton, F.A.C.P., Madison, Wis.

A.M.

9:30–10:20 **Clinical Implications of Recent Studies of Renal Function.**
HOMER W. SMITH, Sc.D. (by invitation), Professor of Physiology, New York University College of Medicine, New York, N. Y.

10:20–10:40 INTERMISSION.

10:40–11:30 **Treatment of Heart and Kidney Disease and of Hypertensive Vascular Disease with the Rice Diet.**
WALTER KEMPNER (Associate), Associate Professor of Medicine, Duke University School of Medicine, Durham, N. C.

Starlight Roof, Waldorf-Astoria Hotel

Presiding Officer
Maurice C. Pincoffs, M.A.C.P., Baltimore, Md.

A.M.

9:30–10:20 **A Survey of the Actualities and Potentialities of Exfoliative Cytology in Cancer Diagnosis.**
GEORGE N. PAPANICOLAOU (by invitation), Professor of Clinical Anatomy, Cornell University Medical College, New York, N. Y.

10:20–10:40 INTERMISSION.

10:40–11:30 **The Collagen Diseases.**
GEORGE BAEHR, F.A.C.P., Clinical Professor of Medicine, Columbia University College of Physicians and Surgeons; Director of Clinical Research and Chief of First Medical Service, Mount Sinai Hospital; New York, N. Y.

Friday, April 1, 1949

Grand Ballroom, Waldorf-Astoria Hotel

Presiding Officer
Charles E. Watts, F.A.C.P., Seattle, Wash.

A.M.

9:30–10:20 **Viral Hepatitis: Problems and Progress.**
JOHN R. NEEFE (by invitation), Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

10:20–10:40 INTERMISSION.

10:40–11:30 **The Use of BAL in the Treatment of Some Forms of Metallic Poisoning.**
WARFIELD T. LONGCOPE, F.A.C.P., Professor Emeritus of Medicine, Johns Hopkins University School of Medicine; Lee, Mass.

Starlight Roof, Waldorf-Astoria Hotel

Presiding Officer
George F. Strong, F.A.C.P., Vancouver, Can.

9:30–10:20 **The Allergy Factor in Disease.**
ROBERT A. COOKE, F.A.C.P., Director of Department of Allergy, Roosevelt Hospital, New York, N. Y.

10:20–10:40 INTERMISSION.

10:40–11:30 **The Response of the Adrenal Cortex to Disease and Injury.**
J. S. L. BROWNE (by invitation), Professor of Medicine, McGill University Faculty of Medicine; Director, University Clinic, Royal Victoria Hospital; Montreal, Can.

PANEL DISCUSSIONS

Topics of intimate interest and practical value to all members of the profession have been chosen. Especially qualified men have been selected as leaders and members of the panel personnel. All panels will be held at the Waldorf-Astoria and are scheduled from Tuesday through Friday, 12:00 M. to 1:15 P.M.

Applications for tickets to panels scheduled in the smaller rooms may be made in advance by members on a regular application form which will accompany the formal program. Tickets will also be available at the Registration Bureau, Silver Corridor, Waldorf-Astoria. Special tickets will not be required for admission to panel discussions in the Grand Ballroom and the Starlight Roof.

Applicants may submit in writing three weeks before the Session, through the Executive Secretary of the College, any questions concerning any phase of the subjects listed. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

PANEL DISCUSSIONS

	Grand Ballroom (Admission by badge; no tickets.)	Starlight Roof (Admission by badge; no tickets.)	Wedgwood Room Office Floor (Admission by ticket only.)	Le Perroquet Suite Fourth Floor (Admission by ticket only.)	Jansen Suite Fourth Floor (Admission by ticket only.)
Capacity	1,000	800	500	250	150
Tuesday March 29 12:00 M. to 1:15 P.M.	**I** **Electrocardiography** Moderator *Paul D. White Boston Emanuel Goldberger New York *Gordon B. Myers Detroit Conger Williams Boston *Charles C. Wolferth Philadelphia	**II** **Peptic Ulcer** Moderator *Henry L. Bockus Philadelphia *Chester M. Jones Boston *Sara M. Jordan Boston *Walter L. Palmer Chicago Stewart G. Wolf, Jr. New York	**III** **Rheumatoid Arthritis** Moderator *Russell L. Cecil New York *Walter Bauer Boston *Edward W. Boland Los Angeles *W. Paul Holbrook Tucson Charles A. Ragan New York	**IV** **Protein Hydrolysates in Nutrition** Moderator *William S. McCann Rochester, N. Y. Frank W. CoTui New York Sidney C. Madden Atlanta John P. Peters New Haven Sidney C. Werner New York *John B. Youmans Chicago	**V** **Management of Thyroid Diseases** Moderator *David P. Barr New York *Edwin B. Astwood Boston *James H. Means Boston Rulon W. Rawson New York Ephraim Shorr New York

	Grand Ballroom (Admission by badge; no tickets.)	Wedgwood Room Office Floor (Admission by ticket only.)	Le Perroquet Suite Fourth Floor (Admission by ticket only.)	Jansen Suite Fourth Floor (Admission by ticket only.)
Capacity	1,000	500	250	150
Wednesday March 30 12:00 M. to 1:15 P.M.	**VI** **Congestive Failure** Moderator *Eugene B. Ferris, Jr. Cincinnati Harry Gold New York *Dickinson W. Richards, Jr. New York *William D. Stroud Philadelphia *J. Edwin Wood, Jr. Charlottesville	**VII** **Antibiotics** Moderator *W. Barry Wood, Jr. St. Louis Harry Eagle Bethesda *Maxwell Finland Boston *Chester S. Keefer Boston Colin M. MacLeod New York *Walsh McDermott New York	**VIII** **Management of Poliomyelitis** Moderator Thomas M. Rivers New York John A. Anderson Salt Lake City David Bodian Baltimore James L. Wilson Ann Arbor Jessie Wright Pittsburgh	**IX** **Medical Diseases of Bone** Moderator *Alexander B. Gutman New York Edward L. Compere Chicago William Parson New Orleans *Edward C. Reifenstein, Jr. New York Isidore Snapper New York

*F.A.C.P.

PANEL DISCUSSIONS—*Continued*

	Grand Ballroom (Admission by badge; no tickets.)	Starlight Roof (Admission by badge; no tickets.)	Wedgwood Room Office Floor (Admission by ticket only.)	Le Perroquet Suite Fourth Floor (Admission by ticket only.)	Jansen Suite Fourth Floor (Admission by ticket only.)
Capacity	1,000	800	500	250	150
Thursday March 31 12:00 M. to 1:15 P.M.	**X** **Hypertension** Moderator Louis Leiter New York Carl A. L. Binger New York Stanley E. Bradley New York Arthur M. Fishberg New York *Henry A. Schroeder, Sr. St. Louis *LeRoy H. Sloan Chicago	**XI** **Diseases of the Liver** Moderator *Richard B. Capps Chicago *Edgar S. Gordon Madison *Thomas N. Horan Detroit John R. Neefe Philadelphia Arthur J. Patek, Jr. New York	**XII** **Renal Diseases** Moderator *George W. Thorn Boston *Maxwell Finland Boston John P. Merrill Boston Edwin L. Prien Boston Donald D. Van Slyke New York	**XIII** **Management of Intractable Pain** Moderator *Roger I. Lee Boston Ernest M. Daland Boston Harris Isbell Lexington, Ky. Bronson S. Ray New York Harry B. van Dyke New York	**XIV** **Hematology** Moderator *Cyrus C. Sturgis Ann Arbor Louis K. Diamond Boston *Charles A. Doan Columbus *Russell L. Haden Cleveland Paul Reznikoff New York
Friday April 1 12:00 M. to 1:15 P.M.	**XV** **Anticoagulants for Thrombo-embolism** Moderator *Nelson W. Barker Rochester, Minn. *Johnson McGuire Cincinnati *Hugh Montgomery Philadelphia *E. Sterling Nichol Miami *Irving S. Wright New York	**XVI** **Newer Aspects of Allergic Phenomena** Moderator *Robert A. Cooke New York Merrill W. Chase New York Alfred Gilman New York Michael Heidelberger New York Paul Klemperer New York	**XVII** **Diabetes** Moderator *Randall G. Sprague Rochester, Minn. *Arthur R. Colwell Evanston *Jerome W. Conn Ann Arbor *Alexander Marble Boston *Franklin B. Peck Indianapolis	**XVIII** **Management of Tuberculosis** Moderator *J. Burns Amberson New York Frank B. Berry New York *H. Corwin Hinshaw, Sr. Rochester, Minn. Kirby S. Howlett, Jr. Shelton, Conn. *James J. Waring Denver	**XIX** **Use and Abuse of Estrogens and Androgens** Moderator Ephraim Shorr New York Earl T. Engle New York *E. Perry McCullagh Cleveland Ira T. Nathanson Boston *Elmer L. Sevringhaus Nutley, N. J.

*F.A.C.P.

THE CLINIC SESSIONS

Clinics and clinical pathological conferences will be conducted on **Tuesday and Thursday only** from 9:15 A.M. to 11:30 A.M., and Morning Lectures will be conducted on Wednesday and Friday mornings, thus eliminating competition between these features of the program. Participating hospitals are listed in the following table, with the days on which they present clinics or clinical pathological conferences. While most of these sessions will be held at the respective hospitals as usual, a number will be offered at the Waldorf-Astoria Hotel. These have been singled out in the table by asterisks.

Adequate accommodations will be provided for all, but admission to most of these sessions will require special tickets which will be issued to members in advance of the Session and to non-members directly at the Registration Bureau in the Waldorf-Astoria Hotel. Application forms for tickets for the clinics and clinical pathological conferences will accompany the formal program to all members.

Emphasis will be placed on clinics in the true sense of that term—that is, patients will be shown and discussed rather than having presentation of formal short papers.

SUMMARY OF CLINICAL PROGRAMS

Tuesday and Thursday Mornings
March 29 and 31, 1949

	HOSPITALS	TUESDAY	THURSDAY
A-1	Bellevue Hospital, Second (Cornell) Medical Division	Clinic	
A-2	Bellevue Hospital, Third (New York University) Medical Division	Clinic	Clinic
A-3	Bellevue Hospital, First (Columbia) Medical Division		Clinic
B	Brooklyn Hospital		*Clinic, 10:30–11:30 (Joint session with F)
C	Flower and Fifth Avenue Hospitals		Clinic
D-1	Goldwater Memorial Hospital, First Division (Columbia University)	*Clinic, 10:30–11:30 (Joint session with N-1)	
D-2	Goldwater Memorial Hospital, Third Division (New York University)		*Clinic
E	Hospital of the Rockefeller Institute for Medical Research	Clinic	
F	Jewish Hospital, Brooklyn		*Clinic, 9:30–10:30 (Joint session with B)
G	Kings County Hospital	*Clinic	
H	Lenox Hill Hospital		Clinic

* This program to be at the Waldorf-Astoria Hotel. All other clinics will be held at the hospital indicated.

SUMMARY OF CLINICAL PROGRAMS—*Continued*

	HOSPITALS	TUESDAY	THURSDAY
J	Long Island College Hospital		*Clinic, 10:30–11:30 (Joint session with P-2)
K	Memorial Hospital		Clinic
L	Montefiore Hospital for Chronic Diseases	*Clinic	
M	Mount Sinai Hospital	Clinic	Clinic
N-1	New York Hospital	*Clinical Pathological Conference, 9:30–10:30 (Joint session with D-1)	Clinic
N-2	New York Hospital	Clinic	
O	New York University-Bellevue Medical Center, Post-Graduate Medical School and University Hospital	Clinic	
P-1	Presbyterian Hospital	Clinic	Clinic
P-2	Presbyterian Hospital		*Clinical Pathological Conference, 9:30–10:30 (Joint session with J)
R	Roosevelt Hospital	Clinic	
S	St. Luke's Hospital	Clinic	
T	Veterans Administration Hospital, Bronx	*Clinic	

* This program to be at the Waldorf-Astoria Hotel. All other clinics will be held at the hospital indicated.

A very wide range of medical topics important to the clinician will be offered. In addition to the various aspects of internal medicine, there will be numerous offerings in allied fields. Opportunities will be afforded for visitors to see patients at close range and to observe hospital methods in New York.

The detailed program of clinics is not published in the ANNALS OF INTERNAL MEDICINE due to its considerable length, but every detail will be published in the formal program and distributed to all members and to non-members on the official mailing list at the Executive Offices of the College approximately six weeks in advance of the session.

Non-members who wish to be placed on the official mailing list are asked to address The Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

ABRIDGED MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 7, 1948

The regular autumn meeting of the Board of Regents of the American College of Physicians was held at the College Headquarters in Philadelphia, Pa., November 7, 1948, with President Walter W. Palmer presiding, Mr. E. R. Loveland, Secretary, and the following in attendance:

Walter W. Palmer, *President;* Reginald Fitz, *President-Elect;* William S. Middleton, *First Vice President;* Maurice C. Pincoffs, *Second Vice President;* Charles E. Watts, *Third Vice President;* William D. Stroud, *Treasurer;* George Morris Piersol, *Secretary-General;* Ernest E. Irons, William S. McCann, T. Grier Miller, Charles F. Moffatt, A. B. Brower, Alex. M. Burgess, Ernest H. Falconer, Cyrus C. Sturgis, Marion A. Blankenhorn, Walter B. Martin, Hugh J. Morgan, LeRoy H. Sloan, George F. Strong, Walter L. Palmer, *Chairman, Board of Governors;* Franklin M. Hanger, *General Chairman, 30th Annual Session.*

The Secretary read abstracted Minutes of the three meetings of the Board of Regents held at San Francisco, Calif., during the 29th Annual Session, April 19–23, 1948, the Minutes being approved as read.

The Secretary then presented the following communications:

(1) From absent Regents—Doctors Charles F. Tenney and David P. Barr;

(2) From Dr. Myron Prinzmetal, Los Angeles, Calif., a former Research Fellow of the College, donating to the College his travel expenses as a guest speaker at the San Francisco Session;

(3) From Mrs. Ernest B. Bradley, widow of our late President, Dr. Ernest B. Bradley, expressing her deep appreciation for the tribute the College had paid to Dr. Bradley through the sending of flowers and a memoriam;

(4) From the "Seventh Pacific Science Congress," New Zealand, embodying an invitation to the American College of Physicians to send a representative to its Congress in New Zealand during February, 1949;

(5) From the Assistant Secretary of the Department of State, thanking the College for its coöoperation in the preparations for the Fourth International Congresses on Tropical Medicine and Malaria, appreciation being extended also to our official representative, Dr. Joseph M. Hayman, Jr., Cleveland, Ohio, who served on the Organizing Committee;

(6) From the American Board of Internal Medicine, informing the College that the terms of two of its representatives on that Board, Dr. Roy W. Scott and Dr. Walter L. Palmer, will expire on July 1, 1949; that both are eligible for re-election for a second term of three years on nomination by the Board of Regents.

On motion by Dr. Reginald Fitz, regularly seconded and carried, Doctors Roy W. Scott and Walter L. Palmer were reappointed by the Board of Regents for additional terms of three years, to July 1, 1952;

(7) From Dr. Ward Darley, College Governor for Colorado, concerning the deductibility of expenses for attending Postgraduate Courses of the American College of Physicians in connection with Federal Income Tax Returns.

The law is so written that expenses for Postgraduate Courses are not deductible on Income Tax Returns, whereas expenses for attending medical con-

ventions are deductible. It was pointed out that the purposes of the Courses of the American College of Physicians are primarily the same as those of its Annual Sessions, namely, the keeping abreast of medical advances in our field. The matter had been placed before the Honorable Eugene Milliken, Chairman of the Senate Finance Committee, who had promised thorough investigation and a later report. It was pointed out that there was essentially no basic difference between a member going to the Annual Session of the College, which we call a "Postgraduate Week," or a member going to one of our one-week courses. The Secretary stated that he had consulted the Treasury Department, inquiring if the name of the Postgraduate Courses might be changed, so that they would be classified the same as conventions, but was informed that this would not be possible. In the discussion that ensued, some pointed out that their Collectors of Internal Revenue had readily allowed deductions for expenses to College Courses, the same as to the Annual Sessions, whereas in other instances the Collector had disallowed such expenses. The matter was left for further information from Senator Milliken:

(8) From the American Council on Rheumatic Fever. The College representatives on this Council were Doctors Hugh Morgan and William D. Stroud. At the last meeting of the Board of Regents Dr. Stroud had reported that the original purpose of the College representation had probably been fulfilled and there was no further reason for continuing representation by the College, and, therefore, the College had withdrawn. The current communication was from Dr. H. M. Marvin, Chairman of the American Council on Rheumatic Fever, who had enclosed a copy of the Minutes of the last meeting of the Executive Committee of the Council and had stated that the work of the Council had been submerged, due to the reorganization of the American Heart Association. He stated that now that the latter had been completed, the Council was planning to proceed at a more rapid pace and requested the American College of Physicians to reappoint delegates to the Council.

On motion by Dr. Hugh J. Morgan, seconded and regularly carried, Dr. William D. Stroud was reappointed the representative of the American College of Physicians on the American Council on Rheumatic Fever.

The President called for the report of the Secretary-General, Dr. George Morris Piersol. Dr. Piersol reported the deaths since the last meeting of this Board of 1 Master; 40 Fellows; 6 Associates, and the names and dates of death were spread upon the Minutes.

Dr. Piersol then reported that since the last meeting of the Board twelve new Life Members had been added, making a grand total of 720, of whom 58 are deceased, leaving a balance of 662, the names as follows:

Aaron Alfred Sprong	Excelsior Springs, Mo.
Walter Howard Wilson	Raleigh, N. C.
Olin S. Allen	Wilmington, Del.
Harold H. Golz	Aramco, Dhahran, Saudi Arabia
Paul Miller Rike	Pittsburgh, Pa.
Theodore S. Heineken	Bloomfield, N. J.
Edward A. Brethauer, Jr.	Pittsburgh, Pa.
Philip Reichert	New York, N. Y.
Jacob L. Tuechter	Cincinnati, Ohio
Gilbert E. Brereton	Dallas, Tex.
Jacob Charles Zillhardt	Binghamton, N. Y.
John W. Wilce	Columbus, Ohio

President Palmer then called for the report of the Executive Secretary, Mr. E. R. Loveland, whose report was as follows:

"I. *New Building Addition:*

This has been completed in a thoroughly satisfactory manner, and it makes available wholly adequate space for the College Staff, with provision for expansion for a long time. The more noisy activity, such as addressographing, duplicating and mailing, has been placed in the basement room. The general stenographic staff is on the first floor, and the second floor provides a fine meeting room, which is being considered for such use as Postgraduate Courses, Regional Meetings, etc. The room, however, has not yet been furnished with chairs, lectern, etc., because the House Committee wishes to consult with the Board of Regents. You will hear about this from the House Committee later.

"II. *Regional Meetings:*

Twenty-three Regional Meetings have been held, or are definitely scheduled, during the current year. The list of the meetings has been duplicated for your information. In general, these Regional Meetings have improved from every point of view; with better programs, larger attendance, more enthusiasm. Dr. Palmer, as President, and various members of the Board of Regents have been highly coöperative in representing the administrative office of the College at these various meetings. We are thoroughly convincd that they make a real contribution to the more active participation of members. The Regional Meetings give many of the younger members opportunities to appear on the programs, whereas they might never have that opportunity at the Annual Sessions. Furthermore, members become better acquainted with one another, and certainly obtain a better understanding of the objectives of the College and the standards of admission. The cost of the Regional Meetings, considering the number thereof, is essentially nominal. For instance, it is estimated that the total cost at the end of this year will be a little over $1,700.00.

"III. *The San Francisco Annual Session:*

I need not refer to the very successful program and to the arrangements at the San Francisco Session, because all of the Regents were there. We had a gross registration of 3,374, which was the third largest registration in the College history, being exceeded only by the Philadelphia (1946) and Chicago (1947) meetings, where the gross registration was 4,037 and 4,410, respectively. It is interesting to note in analyzing the registration, however, that more than half of the registration at the Annual Meetings is made up of guest physicians, senior medical students, exhibitors and ladies. To be sure, many of the guest physicians are guests of members of the College, but there would be no great problem in handling the Annual Meetings of the College if the attendance were limited to members. That remark is made as an observation and not as an intimation that such restriction should be initiated. The cost of the San Francisco Session was greatly in excess of that of any other previous meeting, the gross cost being $34,147.00, compared with Chicago (1947), $23,488.00, and with Philadelphia (1946), $14,865.00. We received the largest gross income from Exhibits at San Francisco of any meeting we have had, but with the expenses deducted, the net income was only $16,774.00. The income from Guest Fees was $1,249.00, and we had a net deficit of over $16,000.00, compared with the net deficit in 1947 of slightly over $5,000.00 and with a net surplus in

1946 of slightly over $5,000.00. The largest increments in expenses at San Francisco were for rental of the auditorium and for the travel expenses of the Regents, Officers and non-member Speakers. You will receive a detailed, comparative cost analysis with the financial statements later on in this meeting.

"IV. *Annals of Internal Medicine:*

The circulation of the 'ANNALS' continues to grow. We are at present printing 12,200 copies per month, with the prospect of having to increase the order in the near future. A year ago the circulation was 11,078. This is more than 100% increase in circulation since 1940. You will find, however, when you receive the report from the Committee on the Annals of Internal Medicine that our printing costs since 1940 have actually increased basically about 100%, and that we face an immediate further increase of approximately 24%. Add to this the consideration that we have been increasing the volume or number of pages of the 'ANNALS' materially, and you will appreciate that our net income is now starting to descend sharply. A year ago, with a thousand less circulation, we had a surplus of over $32,000.00; for the current year, ending June 30, the surplus had decreased to $25,000.00. A year ago the basic printing costs were slightly less than $34,000.00, and for the past year it has increased to over $45,000.00—partly due to the increased basic costs by the printer and partly due to the increased number of copies and the increased size of the journal.

Another observation I would make is that our advertising income is starting downward, although only $1,500.00, during the past year. In the immediate post-war period firms were avaricious in their advertising policies. Now they report that their incomes are decreasing, their expenses increasing, and, therefore, their advertising program being curtailed. We shall have to extend greater effort in attempting to hold up the advertising income.

I do not wish to transgress on the report that will come later from the Committee on the Annals of Internal Medicine, but I would like to observe at this point that all other publishers of medical journals have long since been adjusting their subscription price to the cost of publication. Some medical journals have advanced their subscription prices as much as $5.00 per annum, and most of them have had at least one or more advances in the subscription price during the past two years. The subscription rate for the 'ANNALS' stands today at the same rate it was twenty-two years ago when the journal was much smaller and when the costs were less than one-half of the present rates. I might mention, however, that we have advanced our advertising rates once since the War.

"V. *Candidates for Membership:*

The number of candidates for Associateship now has attained about the same level as that at the outset of the War and the prospects are that there will be an ever increasing number of proposals as time goes along. The number of candidates for advancement to Fellowship is more limited at present than at the outset of the War, because smaller groups of Associates were elected during the war years, and, therefore, there is a smaller number eligible at present to come up for Fellowship. By 1951, however, the number coming up for Fellowship will have resumed its former level and will regularly rise thereafter, unless more restrictive requirements are initiated.

"VI. *Postgraduate Courses:*

This activity for the current year has been on a more or less comparable basis with 1947. The courses still remain extremely popular, and the appreciation of the members appears to grow. We were gratified in receiving a letter from a professor in one of our important medical schools recently, in which he expressed the opinion that the College has attained a topmost position in this type of postgraduate education in the country. Perhaps we have been too prone to fail to attach adequate importance to this activity of the College, because the courses are short and scattered. The report of the Committee will reveal many interesting features of this program.

"VII. *Membership Roster:*

During the past summer we published, in accordance with directions of the Regents, a new and revised Membership Roster. It cost, however, nearly $4,000.00, which includes postage of some $600.00. There continues to be a desire and need for a complete College Directory, but the publication of such a Directory under present conditions would involve a cost at least of $17,000.00, a figure which causes us to consider seriously the propriety of publishing a Directory during 1949. That is a matter that must be determined by the Board of Regents and probably should not be discussed at this point, but in connection with the report of the Committee on Finance and the adoption of budgets for 1949."

Mr. Loveland then introduced a discussion of the advertising policies, and stated the "ANNALS" was sometimes criticized by advertisers because of its highly restrictive policy in refusing the acceptance of advertising of any pharmaceutical product which has not yet been accepted by the Council on Pharmacy and Chemistry.

Dr. Piersol, Chairman of the Committee on Advertising, said he had discussed the matter at length with Mr. Pindar, who is handling the advertising for the "ANNALS," and pointed out that there are some of the large, reputable drug houses who, for instance, manufacture penicillin, but who can no longer make a profit from advertising this product as "penicillin," because the name does not in any manner distinguish their product from that of their competitors. Yet, the regulations of the Council may prevent the manufacturer from using a special trade name for his brand. If such were done, his brand of penicillin would not be acceptable for advertising in the "ANNALS," or any of the other journals which support the Council on Pharmacy and Chemistry. Dr. Piersol expressed the belief that there is some question whether the average physician actually pays any attention to whether some of the better preparations are either approved or disapproved by the Council. He suggested that this complicated subject should be carefully considered, and possibly some modification made, and that a committee be appointed to explore the whole subject before the next meeting of the Regents, and that they be requested to bring in a report with more factual data on which the Regents might take some action to modify the present rule.

On motion by Dr. George Morris Piersol, regularly seconded and unanimously carried, his recommendation was approved.

The Board at this point took up a discussion of that part of the Secretary's report concerning the publication of a Membership Roster or of a completely revised Directory during 1949. It was pointed out that there is a persistent request among members for the republication of a full Directory of the College. The College has been a rather generous organization. Although its dues are comparatively small, it has given in the past without charge to its members the journal, the Membership Roster or Directory and many and all other publications. Numerous other societies retain the dues exclusively for the maintenance of its organization and annual meetings and

charge their members for their publications. Although operating costs have increased nearly 100 per cent, the dues, though increased 33⅓ per cent over the "depression" period, are still at the same level as in 1929. The thought was advanced by the Secretary that while the Membership Roster might continue to be given to members without charge, the Directory, to cost between $17,000.00 and $20,000.00, might be sold to members at pro rata cost price on a pre-publication order plan, or at approximately $4.00 per copy, postpaid. He pointed out that such a price was small and most reasonable in comparison with charges made for ordinary directories. The matter was left for further consideration at the time of the receipt of the report of the Committee on Finance.

President Palmer then called for the report of the Committee on Credentials, Dr. George Morris Piersol, Chairman.

Dr. Piersol reported that the Committee on November 5-6, 1948, had reviewed the credentials of 204 candidates for Associateship and 131 candidates for Fellowship. Of this number, the Committee recommended the election to Fellowship of 81 candidates, and of the election to Associateship of 215 candidates, 11 of whom had actually been proposed for direct Fellowship.

The recommendations for election were approved by formal resolution, and the names of 81 new Fellows and 215 new Associates were spread upon the Minutes.

Dr. Piersol further presented the names of Associates, elected during the war years, who were entitled to extension of time to qualify for Fellowship, and recorded the names of Associates who had to be discontinued on the Roster, because of failure to qualify for Fellowship.

A summary report on the candidates elected to Associateship on November 20, 1943, was as follows:

Already Advanced to Fellowship	87
Resigned	1
Dropped for Failure to Qualify	13
Term Extended due to Military Service	37
Total, Candidates elected November 20, 1943	138

Continuing his report, Dr. Piersol stated that the Committee on Credentials and the Executive Committee of the Board of Regents would convene a day earlier at the New York Annual Session in March, 1949, for the purpose of reviewing two proposals under consideration—(1) that the College be restricted to Internists; (2) that certification be a prerequisite for Associateship—with the hope that out of such a meeting would come solid recommendations upon which the Board of Regents may act.

The Committee on Credentials had received a communication from an Associate, elected May 12, 1946, who due to graduation from a medical school in Germany had been refused admittance to the examinations of the American Board of Internal Medicine, and who, therefore, will be unable presumably to qualify for advancement to Fellowship. The Committee stated that it knew of no remedy that the College could offer to assist this candidate.

The Committee also received a communication from a physician in Manila, who requests that something be done to make physicians from the Philippine Islands eligible for membership in the College. Dr. Piersol pointed out that it has been a long established policy to restrict membership to citizens of North America, and since the Philippine Islands are wholly outside of our territory now, we can only inform the gentleman that physicians from that Country are not eligible in our College at the present time.

On recommendation of the Committee on Credentials, unanimously approved by the Board of Regents, Dr. Christian Bateman Luginbuhl, of Des Moines, Iowa, was reinstated as a Fellow of the College.

The complete report of the Committee on Credentials was accepted as a whole.

Dr. William D. Stroud, Chairman, reported for the House Committee.

The entire building appropriation of $55,153.87 had been expended, but actually some funds had been used for semi-furnishing items, such as venetian blinds, window shades, screens, plastic flooring, landscaping, etc. He reported also the purchase of some items of equipment, amounting to $656.35, approved by the Committee.

He said the Second Floor Meeting Room could readily be equipped to accommodate Postgraduate Courses and Regional Meetings of the College, and that the House Committee was prepared to recommend the purchase of chairs, lectern, coat and hat racks, and other necessary equipment. The Committee presented specific recommendations for needed items of plumbing, painting and papering, totalling an estimated expense of $1,260.00.

The Committee also recommended that the property adjoining the College Headquarters, owned by the College, shall have such repairs and replacements as are minimally required for the time being.

He reported that the Committee had examined the budget for the College Headquarters for 1949, and recommended its adoption.

By formal resolution the report of the House Committee was received, and its recommendations approved.

President Palmer then called for the report of the Committee on Masterships, Dr. William S. Middleton, Chairman.

"The Committee on Masterships met yesterday, reviewed the subject of the qualifications for Masters and was agreeable to the general opinion that these Masters should represent only individuals who have been outstanding in the field of medicine, who have given materially to the College and who have attained not only national but international reputations. The Committee, furthermore, talked over the question of the appearance of the nominees at the Convocation at which the distinction would be awarded, and it was the feeling of this Committee that, unless there are unusual circumstances, making it impossible for the designated individuals to appear, such Masterships should not be granted. This imposes upon the Officers of the College the decision as to what constitutes an extenuating circumstance. It is perfectly apparent that if a Mastership in the College is to attain or to maintain the dignity of an honorary degree, in keeping with the practice of recognized institutions of learning, the honorary degree shall not be granted in absentia.

"The Committee recommends for the distinction of Masterships in 1949:

Dr. George Dock ..... Altadena, Calif.
Dr. Elliott P. Joslin ..... Boston, Mass.
Dr. Jonathan C. Meakins ..... Montreal, Que., Canada
Dr. Virgil P. Sydenstricker ..... Augusta, Ga.
Dr. James J. Waring ..... Denver, Colo."

After general discussion, on motion by Dr. William S. Middleton, seconded and regularly carried, the report and recommendations of the Committee on Masterships were approved.

Dr. Ernest E. Irons, as Chairman, made the following report for the Committee on Public Relations:

"I. *Communications:*

"(*a*) Gorgas Memorial Institute of Tropical and Preventive Medicine.

The College is interested in this because our President is an ex officio member of the Institute; otherwise we have no special

interest. The report from the Institute is received and the acknowledgment of the report is sufficient; no action recommended;

"(*b*) World Medical Association, Dr. Louis H. Bauer, F.A.C.P., Secretary-Treasurer.

Dr. Bauer wrote to President Palmer. The World Medical Association was formed originally through the action of English, French, American and Canadian physicians. There are both organizational and individual memberships. Each member will receive a certificate of membership and will receive the publications of the World Medical Association and of the United States Committee. Organization members may also submit problems of international interest or their particular fields for study by the Association. In the early organization of the World Medical Association it was recognized that most of the nations of Europe would be limited in their finances, and that some method might have to be devised to finance any significant program. Thus a United States Committee was formed as an auxiliary financial agent. On the Board of this Committee are five or six doctors and four or five representatives of manufacturing interests. It has required something over $50,000.00 to finance this organization, including the financing of its headquarters in the New York Academy of Medicine under the Secretary-Generalship of Dr. Louis H. Bauer.

The American Medical Association, the International College of Surgeons, the Mayo Clinic, the American Red Cross and the National Foundation for Infantile Paralysis, and numerous organizations allied to medicine, have become members. The United States Committee would be glad to have the American College of Physicians to become a sustaining member, and it is hoped that those who accept membership will remain members for at least five years. The members enumerated above have each agreed to contribute $2,000.00 a year; others are contributing from $1,000.00 to $10,000.00 a year. The College is being requested to contribute an amount in proportion to its membership and financial status, the exact amount to be determined by the Board of Regents. In so doing, the College may feel that it is helping to improve medical health standards throughout the world, and to improve international medical relations, and to be able to use the facilities of the World Medical Association for investigation of some problems within the field of our College.

The World Medical Association has the blessing of our State Department and is an auxiliary medical effort, which will take up questions that the World Health Organization cannot consider by reason of its political union with the United Nations.

Our Committee recommends to the Regents that the American College of Physicians participate in the World Medical Association and contribute the amount of $2,000.00 per year for five years."

Dr. Irons moved approval of the recommendation, and it was seconded and opened for discussion, but after extended discussion, the motion was laid on the table for further consideration later in the meeting, at the time of the report of the Committee on Finance.

Dr. Irons continuing his report:

"(*c*) Ada P. McCormick, Editor & Publisher of 'Letter'—telegram concerning the Kinsey report.

The Committee recommends merely that the telegram be filed.

"(*d*) The Pennsylvania Radiological Society.

The correspondence includes the resolution of May 22, 1948, of the Pennsylvania Radiological Society, directed to the House of Delegates of the American Medical Association. The Committee wishes to express itself in sympathy with the importance and complexity of this problem. In keeping with the previous policies of the College, however, the Committee feels that action in the problem should be referred to the American Medical Association. The problem referred to is one involving support of radiologists in their controversy with hospitals.

"(*e*) Prof. A. Gigon, Basel, Switzerland, regarding the organization of the International Society of Internal Medicine.

The Committee reaffirms the opinion expressed at a previous meeting of the Board of Regents to the effect that inasmuch as the World Medical Association is in process of organization and function, there is no immediate reason for promoting another organization at this time.

"(*f*) Riverside County Medical Association, concerning the advertisement in the local newspaper by a Fellow of this College.

The Committee regards the advertisement as a breach of ethics which a Fellow of the College should not engage in, and recommends that a letter be sent, expressing this view, but asking for any explanation he may have in the matter."

On motion by Dr. Irons, seconded and regularly carried, this section of the report was approved.

"II. *Fees and Dues Cases:*

Dr. Irons reviewed the cases of 3 Fellows who had retired from practice or other remunerative medical work, due to physical disability, and on recommendation of the Committee, with the approval of the Regents, dues were waived beginning January 1, 1949, and until recovery and resumption of work.

"III. *Resignations:*

The Committee has reviewed the resignations of Dr. Morgan J. Foster (Associate), Cedar Rapids, Iowa; Dr. William L. Wheeler (Associate), New York, N. Y.; and Dr. Horace Pettit (Associate), Gladwyne, Pa., and recommends acceptance of all three."

On motion by Dr. Irons and duly carried, this section of the report was approved.

"IV. *Establishment of Honorary Fellowships:*

The Committee has considered the establishment of Honorary Fellowships, and recommends to the Regents that a category of Honorary Fellowships be approved in principle by the College. This matter comes up in connection with a request from Dr. Noble Wiley Jones, and others, for the College to provide Honorary Fellowships for distinguished persons from

other countries. The Royal Australasian College of Physicians has honored Dr. Noble Wiley Jones and Dr. Hugh J. Morgan with similar Fellowships. If the Board of Regents approves of this recommendation, the Committee on Constitution and By-Laws will provide the amendments."

There followed long discussion of the matter, and questions were raised as to whether an Honorary Fellowship would be granted in absentia, or whether the candidate would have to be present; whether it might be limited to especially distinguished guests invited to appear on our Annual Session programs; whether it be considered merely a distinction conferred, because of accomplishment, on some foreign physician; and whether the College would be subjected to undue pressure creating difficult situations; whether it should be limited to a very small number of individuals. Dr. Irons was asked to submit the wording of the amendment to the By-Laws in case the proposal was adopted.

Dr. Irons, also Chairman of the Committee on Constitution and By-Laws, presented the following recommendation:

"The Committee on Constitution and By-Laws recommends that Article IV of the Constitution shall be amended by changing the introductory sentence to read 'Members of the American College of Physicians shall be of three classes: (*a*) Fellows; (*b*) Masters; and (*c*) Honorary Fellows,' and by adding a new section, 'Section (*c*). Honorary Fellows. Honorary Fellows shall be internists, members of the medical profession of countries other than the United States or Canada, who on account of personal character, positions of honor and influence, or eminence in the practice of internal medicine or in research, shall be recommended by the Committee on Masterships to the Board of Regents. Honorary Fellows shall not have the right to vote or to hold office.'"

"The Committee also recommends amending Article IV, Section (*b*) by reversing the order of the words 'influence and honor' to read 'honor and influence.'"

"The Committee also recommends amending Article VI of the By-Laws: amending the title to read 'Election of Masters and Honorary Fellows'; numbering the first paragraph '(*a*),' and adding paragraph '(*b*) The Committee on Masterships may also present to the Board of Regents nominations for the election of Honorary Fellows. Not more than two Honorary Fellows shall be elected in any calendar year.'"

On motion by Dr. Irons, on behalf of the Committee on Public Relations, and duly seconded, a resolution was adopted approving of Honorary Fellowships and authorizing the proper amendments to the Constitution and By-Laws. Then a series of formal resolutions were adopted approving of each amendment to the Constitution and By-Laws. It was further recorded that, as a regulation of the Board of Regents, no dues shall be exacted from Honorary Fellows.

"V. *Eligibility for College Membership:*

"(*a*) Veterans Administration Physicians.

Heretofore Veterans Administration Physicians were blocked from admission to the American Board of Internal Medicine examinations in those localities where they were not eligible for membership in county and state medical societies and the American Medical Association. So far as the Committee on Public Relations knows at present, Veterans Administration Physicians can now join the American Medical Association by special action of that body, and, therefore, can be admitted to the examinations of the American Board of Internal Medicine.

Unless other evidence develops, the Committee recommends no action.

"(*b*) Physicians from North American Countries, other than Canada and the United States.

Heretofore these physicians were blocked from membership in the College, because they are not eligible for admission to the examinations of the American Board of Internal Medicine, due to lack of membership in the American Medical Association or the Canadian Medical Association.

This is a defect possibly in the regulations of the American Board of Internal Medicine and of the American College of Physicians. The Committee suggests that this matter be deferred until further information can be obtained from the American Board of Internal Medicine. The Committee points out that Direct Fellowship in the College is still available to distinguished physicians from such countries.

"VI. Fees and Dues of Medical Officers in the Army, Navy, Public Health Service and Veterans Administration (referred to the Committee on Public Relations by the Board of Regents at San Francisco, April 20, 1948).

A number of schedules of salaries available to the various ranks in the Army, Navy, Public Health Service and Veterans Administration, and salaries paid to full-time teachers of medicine has been studied.

The Committee recommends that, under interpretations by the Board of Regents of the By-Laws, pages 14 and 15 of the informative booklet, the two paragraphs under 'Class D—Special cases falling in one or more of the above classes (Class A, practicing clinicians; Class B, whole-time teachers or research workers with salaries of $5,000.00 or more; Class C, whole-time teachers and research workers with salaries of less than $5,000.00)' shall be deleted, and that Medical Officers in the Army, Navy, Public Health Service and Veterans Administration be considered under Classes B and C.

The Committee also recommends that minimal dues be increased from $10.00 to $12.00, thus revising Class B and Class C accordingly."

On motion by Dr. Irons, duly seconded and carried, this section was approved, and the report was adopted as a whole.

Dr. Reginald Fitz, Chairman, presented the following report for the Committee on Fellowships and Awards:

"Our Committee has remembered the basic purposes of Research Fellowships. The By-Laws state that Research Fellowships are established 'to promote and advance clinical research' and are designed especially for the benefit of young physicians who are in the early stages of preparation for a teaching or investigative career in medicine.

"This year we have reviewed the records of thirty-three (33) applicants, and believe that eight (8) deserve Research Fellowships from the College. These candidates are:

James K. DeVore; 25; a graduate of Oklahoma in 1947; a veteran; who hopes to work under Dr. Irvine H. Page, at the Cleveland Clinic, on general problems related to hypertension; $2,200.00.

Stefan S. Fajans; 30; a graduate of Michigan in 1942; a veteran; who hopes to work under Dr. Jerome W. Conn, University of Michigan, upon physiological mechanisms capable of stimulating or depressing the Islets of Langerhans; $3,000.00.

Horace W. Gerarde; 29; a graduate of Wisconsin in 1948; who hopes to work under Dr. N. A. Womack, University of Iowa, on the histochemistry of certain liver diseases; $3,200.00.

John C. Laidlaw; 27; a graduate of Toronto, 1944; a veteran; who hopes to work under Dr. F. G. Young, University College, London, England, on metabolism of certain cholinesterase inhibitors in relation to myasthenia gravis; $2,200.00.

James Metcalfe, Jr.; 26; a graduate of Harvard in 1946; a veteran; who hopes to work under Dr. E. M. Landis at Harvard on the dynamics of the circulation under various conditions; $3,200.00.

Samuel Moore Peacock, Jr.; 26; a graduate of Pennsylvania in 1948; who hopes to work under Dr. Robert Hodes at the University of Pennsylvania on the cytochemistry of nervous tissue during growth and other physiological activity; $2,200.00.

Jack L. Strominger; 23; a graduate of Yale in 1948; who hopes to work under Dr. O. H. Lowry at Washington University on the microchemistry of the brain tissue; $2,200.00.

Edgar Woody, Jr.; 29; a graduate of Johns Hopkins in 1944; a veteran; who hopes to work under the Departments of Medicine and Pathology at Vanderbilt University on the combined effect of potassium iodide and streptomycin in experimental tuberculosis; $2,200.00.

"Of these young men, the Committee has selected Dr. John C. Laidlaw as the Alfred Stengel Research Fellow, since in their judgment he offers greatest promise of attaining unusual distinction in investigation, teaching and as a clinician.

"The stipends recommended for these fellows will vary to meet individual needs. It may be of some interest to note that none of the thirty-three (33) applicants expressed any interest in working on isotope problems.

"The Committee asks that $17,400.00 be set aside for Fellowships in the 1949 Budget, and for permission to use an unexpended sum of $3,000.00, freed in 1948 by a Fellowship granted, but not accepted.

"The Committee is gratified to report that six Fellows appointed to begin their Fellowships on July 1, 1948, are happily at work, and that follow up notes on previous Fellows continue to prove the value of Fellowships.

"The Committee has selected to receive the John Phillips Memorial Award for 1949 Dr. Edwin B. Astwood, Professor of Experimental Medicine at Tufts Medical College, Boston. His work in introducing antithyroid drugs represents an outstanding piece of work in Internal Medicine; it has had a direct bearing on the advancement of Clinical Science by opening numerous channels of exploration to other investigators.

"The Committee, after obtaining the advice of the President and Fellows consulted, because of their expert knowledge in the field of Preventive Medicine, nominates to the Board of Regents as second recipient of the James D. Bruce Memorial Award Dr. Stanhope Bayne-Jones, of New York. His many talents and his broad interests in a variety of aspects of public health make him seem a suitable candidate.

"Through Dr. Sturgis the Kellogg Foundation has made an interesting approach to the College. The Committee considers the matter of considerable importance, and has directed the Chairman to ask the Regents to allow Dr. Sturgis the privilege of the floor, so that he may present to the Board the Foundation's proposal."

On motion by Dr. Reginald Fitz, duly seconded and unanimously carried, all recommendations of the Committee on Fellowships and Awards were approved, and the report adopted as a whole.

Dr. Fitz then introduced a discussion of a proposal by the W. K. Kellogg Foundation, to set up American College of Physicians' Latin-American Fellowships, the matter having first been presented to Dr. Fitz by Dr. Cyrus C. Sturgis.

Dr. Sturgis explained that the Kellogg Foundation, of Battle Creek, Mich., has been established for about twenty years, has assets of some sixty-six million dollars, and has as its primary interest the medical betterment of the world. Their activities

began in Michigan and spread over the United States and now through Mexico, Central and South America. Dr. Benjamin G. Horning, Director of the Division of Medicine of the Kellogg Foundation, would like the College to take six young men from Central and South America who are interested in Internal Medicine for one or more years' fellowships in the United States, after which they will be guaranteed teaching positions in their home lands. These men thus selected would have their way paid partially by the State Department, and the Kellogg Foundation would pay their fellowship expenses. Many of them would first be taken to the University of Michigan for language study for a month or two, and then assigned to the formal fellowships for a study period of a year, and the program would start in the autumn of 1949, if approved by the College. The selection of the candidates would be made by Dr. Horning through personal contact with the various medical schools and hospitals in the countries from which the candidates come, and the College would have the right to select six of the group of nominees. Dr. Sturgis pointed out that in the past there has been some criticism because candidates for medical training from South and Central America have been largely unsponsored, unasked and precipitated upon us, creating quite a task. Some have been unable to speak English; some of them have not had adequate scholastic standing; and some institutions, therefore, have not had satisfactory experience with them. Under this plan they would be formally sponsored by the College, the Kellogg Foundation and the State Department; they would be carefully selected; and they would be carefully supervised while in America. It would cost the College nothing financially, but would require time in the selection of the men and in the location of institutions where they will be accepted. Dr. Sturgis recommended the proposal as a means for the American College of Physicians to extend its influence. He pointed out that the Kellogg Foundation is interested in very many things in common with the College, such as postgraduate education.

In the discussion that followed, Dr. Walter L. Palmer suggested that the required period for the study of English be increased to three or four months, and that the term of the fellowship should in many instances be longer than a year. Dr. Palmer had had a considerable experience with fellows from the Latin-American countries and felt that they often had inadequate time for medical training after attaining a working knowledge of English. He considered it utter folly to bring these men to America unless they will have adequate time for necessary training.

Dr. Sturgis expressed the opinion that the appointments by the College be made from year to year, and expressed the feeling that the Kellogg Foundation would be glad to extend fellowships in individually merited cases for two, three or more years.

Dr. Maurice C. Pincoffs pointed out that heretofore the American College of Physicians' regular Research Fellowships were awarded to men who could themselves locate acceptable institutions that would accept them for study, and the College would pay the bill, whereas in this case the policy is reversed, the College is to find them the place to work and the Kellogg Foundation will pay the expenses.

Dr. William S. Middleton said that he had reviewed the Kellogg Foundation's proposal and believed it entirely sound, with certain limitations, such as pointed out by Dr. Pincoffs, and he predicted the program could readily be made effective.

On motion by Dr. Cyrus C. Sturgis, duly seconded, a resolution was adopted, providing that the Board of Regents approve of the proposal in principle; also on a motion by Dr. Sturgis, duly seconded, a resolution was adopted that the matter be referred to the Committee on Educational Policy for recommendations as to procedure.

Dr. Hugh J. Morgan, Chairman, presented a brief report of the work of the American Board of Internal Medicine. He said the basic mission of the Board is being carried out, that the Board is contributing to the elevation of standards and the practice of Internal Medicine in this country. He spoke of the need for some agency to survey the qualitative needs of the country with relation to internists, and such a survey would enable the Board to operate far more intelligently. The Board is

conscious, he said, of its responsibilities. Hospitals throughout the country, in many instances, insist upon certification before staff appointments are made; many medical schools require certification before appointment on the faculty or the staff. The Board also, he stated, had added responsibilities thrust upon it by the College, because certification is one of the College requirements for membership. The technical operation of the Board, with respect to its two types of examinations, is in a satisfactory state; 1,180 candidates had taken the written examination during 1948; about 66 per cent passed and about 34 per cent failed; 730 candidates had taken the oral examination, and about 75 per cent had passed and 25 per cent failed.

Dr. Morgan reported also that the Board had recommended to the Council on Medical Education and Hospitals of the American Medical Association that that Council should appoint consultants throughout the country to inspect hospitals for the determination of their qualifications for resident training programs. The Council has not been able up to the present, he said, to provide an adequate mechanism for hospital inspection. That inefficiency had reflected itself on the operation of the Board, for the Board has been asked to approve or disapprove hospitals for resident training, but the Board has no operating facility for that work. The Conference Committee, consisting of representatives from the College, the Board and the Council, has been reactivated, and both the Board and the College will assist in the nomination of consultants to help the Council in its program.

Dr. Ernest E. Irons inquired whether or not the American Board of Internal Medicine could properly help share the expenses of the hospital program, and Dr. Morgan expressed the opinion that the Board would be willing, within its economic ability.

By resolution Dr. Morgan's report on the American Board of Internal Medicine was accepted.

Dr. William S. Middleton, as Chairman, reported for the Committee on Educational Policy and for the Advisory Committee on Postgraduate Courses. He stated that the attendance at the College courses for the year 1948 had been most gratifying —485 for the spring courses and 478 for the autumn courses. It has been customary, he said, to collect reports from the registrant concerning each course, in an attempt to obtain constructive criticism for the improvement and extension of the postgraduate program. The Committee believed that it would be more effective if in the abstracts of the report the names of the writers be excluded, the feeling being that there may be some hesitancy on the part of an individual to comment unfavorably on the content, presentation of given material, etc. The Committee had observed, however, that all criticism has appeared to be perfectly open and constructive, and certainly helpful. The Committee had reviewed proposed courses for the near future, and announced the schedule for the spring of 1949 (already previously published).

Dr. Middleton then stated that the Committee had recommended that the American College of Physicians go on record as strongly supporting the position of the American Board of Internal Medicine in its position that fundamental certification in Internal Medicine must continue to be a prerequisite for later certification in several of the sub-specialties of Internal Medicine.

The Committee also was of the opinion that the duplicating of subject material at the graduate courses offered by the College cannot be reproduced for the registrant or for circularization. Every member of the Committee present who had experience in this field believed that it would be a deterrent to effective teaching, a deterrent to the organization of courses in the future, to require prior preparation for reproduction of subject material. The Committee had information at hand indicating that some of the directors would withdraw from the program if the College thrust upon them responsibility for the reproduction of the subject material in their courses—a chore so great that it would preclude the possibility of their directing courses. The Committee felt, however, in individual cases the College might grant permission for the

reproduction of the material, such as in the case of the course in Gastro-enterology at Philadelphia during December, 1948, under Dr. Henry L. Bockus, where overtures and assurances from a local publishing house had been received, stating their willingness to underwrite the publication of this course.

Dr. Maurice C. Pincoffs raised a question in connection with the publication of course subject material, saying that he interpreted it as meaning that subject material would not appear as a publication sponsored by the College, but as a publication sponsored by the individual.

On motion by Dr. William S. Middleton, duly seconded, the report of the Committee on Educational Policy and of the Advisory Committee on Postgraduate Courses was adopted.

Dr. T. Grier Miller, Chairman, presented the report for the Committee on the Annals of Internal Medicine, stating that the cost per page for printing the journal had been increased 23 per cent as of November 1, thus making an average of 94 per cent increase since 1940. Although the number of pages per year had increased only by 122, the overall cost, exclusive of the new 23 per cent rise, had increased from $21,800.00 to $45,300.00—almost 99 per cent. Because of a greatly increased circulation, however, a surplus had thus far been maintained, although the surplus for Volumes XXVII–XXVIII had decreased some $7,000.00 from that for the two immediately preceding Volumes, XXV–XXVI. The new increase in printing costs, Dr. Miller predicted, would reduce this surplus an additional $10,000.00 in 1949—still further, if further costs are imposed or advertising is curtailed. He pointed out that the subscription price of other medical journals has been increased from 16⅔ per cent to 60 per cent, whereas the ANNALS' subscription rate has never been changed since the journal was founded in 1926. The Committee on the Annals of Internal Medicine therefore recommended that the basic subscription rate be raised from $7.00 to $10.00 for domestic circulation and to $11.00 for foreign circulation, and that in the case of members of the College, $9.00 of their dues shall be assigned to the ANNALS account.

The Committee on the Annals also recommended that personal news items shall be omitted from the journal, and the News Section largely restricted to Minutes of the Boards and Committees, notices of Regional Meetings and Postgraduate Courses, and other items of national importance to the College.

The Committee also recommended that books selected by the Editor as suitable for Review be submitted to competent Fellows or Masters of the College throughout the country, who shall be requested to prepare critical reviews promptly and without compensation, their names to be published in full in connection with the review.

Finally, the Committee expressed its commendation of Dr. Maurice C. Pincoffs, the Editor, for his efficient management of the editorial affairs of the journal.

The report and recommendations of the Committee on the Annals of Internal Medicine were unanimously approved.

Dr. Maurice C. Pincoffs, as Editor, presented a brief report, stating that the quality of material received for the ANNALS in the last year had greatly exceeded that of previous years.

Dr. LeRoy H. Sloan reported for the Conference Committee on Graduate Training in Medicine, stating that he had met with the Council on Medical Education and Hospitals, and with the American Board of Internal Medicine, and had held conferences with Dr. Donald Anderson, Secretary of the Council. The actual accomplishments of the Committee had been the reactivation of the coöperative plan among the Council, the American Board and the College, with two members of each agency forming a committee. They had been concerned chiefly with the matter of approval of hospitals for residencies in Internal Medicine. The Committee believed that if an approved list bearing the stamp of approval of the College, the Council and the Board were published, it would certainly carry much more weight than otherwise.

Dr. Sloan stated that the Council had approved the employment of part-time in-

spectors; that there remain over a thousand hospitals to be visited; that the Council will soon cover four hundred of these through their full-time inspectors, and that it will employ part-time inspectors to take care of an additional four hundred. The cost is estimated at from $25,000.00 to $37,500.00, this covering inspection of all departments and not merely the Department of Medicine.

Dr. Reginald Fitz inquired whether Dr. Sloan had any specific recommendations as to how much of the cost the College should be willing to contribute. President Palmer replied that the College was not in a position to make any specific commitment, because the cost has not yet been reasonably clearly determined.

Dr. Walter B. Martin presented the proposal that a hospital should contribute the cost of its inspection, just as do physicians who are taking certification board examinations, and Dr. Sloan accepted the thought as an excellent suggestion.

Dr. Fitz pointed out that the general plan is that the Council on Medical Education and Hospitals in various areas will appoint inspectors and consultants, vouched for by the College, and possibly utilizing in some manner the College Governor for that area, men who are capable of giving a fair and impartial inspection of hospitals. Such a program of inspection, with the participation of the Council, the College and the Board, will really mean something. Dr. Fitz said that it will naturally require a complicated machinery, and that the inspectors who give their time, whether it be a day or several days, should be entitled to some sort of compensation.

Dr. Fitz presented the suggestion that the College contribute $5,000.00 to the hospital inspection program, expenditure to be made subject to the approval of the Committee on Finance.

Dr. Hugh J. Morgan thought the suggestion somewhat premature, in view of the fact that there are many facts not yet established, namely, what the program will actually cost, what its final details will be, when it will get into operation, how much the College is actually able to contribute. Dr. Morgan further pointed out that the Council on Medical Education and Hospitals is also interested in the other specialties of medicine, including surgery itself, and that the American College of Surgeons and the American Board of Surgery might have some interest in the program. He intimated that the program for Internal Medicine and its proportionate cost should be established, and the proportionate responsibilities of the Council, of the American Board of Internal Medicine and of the American College of Physicians should then be determined.

On motion by Dr. Reginald Fitz, duly seconded and carried, a resolution was adopted referring the matter to the Conference Committee on Graduate Training in Medicine, with the request that that Committee report back to the Board of Regents or to the Executive Committee of the College, concerning not only needed finances, but more specific details as suggested in the preceding discussion.

A resolution was adopted accepting Dr. LeRoy H. Sloan's report.

Another resolution, made by Dr. Ernest E. Irons, and duly seconded, was adopted, providing that the Board of Regents of the College request the American Board of Internal Medicine to explore their possibilities of contributing toward the hospital inspection program.

Dr. Maurice C. Pincoffs, as Chairman, reported for the Committee on the Alfred Stengel Memorial Award. Dr. Pincoffs reviewed the purposes and regulations of the Award, saying that it was established by the late Dr. James D. Bruce "to be awarded periodically by the President at a Convocation of the College to a Fellow, and preferably to a Fellow who has served as an Officer, Regent or Governor, who by virtue of his loyalty and service to the College deserves an honor from it that is unique. Besides loyalty and service to the College, the candidate shall have displayed an outstanding influence in maintaining and advancing the best standards in medical education, medical practice and clinical research, in perpetuating the history and traditions of medicine and medical ethics, and in upholding the dignity and the efficiency of

internal medicine in its relation to public welfare." Recipients shall be chosen by the Board of Regents at a regular meeting prior to the Convocation at which the Award is to be made. At least three and not more than five nominations shall be presented to the Board of Regents. The Committee nominated three candidates, voting was done by secret ballot and the recipient was selected, subject to announcement at the 1949 Convocation.

President Palmer then introduced a discussion and report on the program for the 30th Annual Session, New York, N. Y., March 28–April 1, 1949. He distributed the tentative list of topics and speakers. The Committee had selected a large number of topics and subjects which would be of most interest to the College members, and then proceeded to try to obtain the most able and best man to speak on each topic.

Dr. Franklin M. Hanger, General Chairman, discussed at considerable length the general plans for the 30th Annual Session, including particularly the program of panel discussions, hospital clinics and entertainment. Some new features will be introduced in the program, including having certain clinics and clinical-pathological conferences held at the hotel, although the usual hospital clinics in the hospitals will be continued in the case of convenient institutions. Dr. Hanger further discussed the exceedingly attractive program of entertainment for visiting women. He asked particularly for the advice of the Board of Regents with regard to entertaining the wives of Officers, Regents and Governors on Sunday evening, March 27, when the members of those Boards will be at their annual dinner. At the San Francisco Annual Session, the Women's Entertainment Committee paid for the expenses of such a dinner for the wives of Officers, Regents and Governors, but the current budget is inadequate to do the same at New York.

After general discussion among the Regents, it was agreed that the Women's Entertainment Committee arrange for the dinner, but that the Officers, Regents and Governors shall purchase tickets for their wives, covering the cost.

Dr. Ernest E. Irons, as Chairman of the Joint Committee for the Coördination of Medical Activities, reported that that Committee, with its related representatives, continues to meet, and discusses problems of current interest, such as veterans housing, and other matters affecting medicine and public welfare.

Dr. William D. Stroud, Treasurer, presented the following report:

"The report of the Treasurer is merely supplemental to that of the Committee on Finance. The cash balance on October 1, 1948, was as follows:

Endowment Fund	$ 1,377.83
General Fund	74,110.11
	$75,487.94

"It is estimated that there will be some $38,000.00 additional receipts between October first and the end of the year. The Committee on Finance will make recommendations concerning the investment of surplus funds not required for operations, and it will also report the record of security transactions since the last meeting of this Board.

"The present security holdings of the College are as follows:

	Book Value	*Market Value*	*Appreciation*
A. Blaine Brower Fund	$ 2,500.00	$ 2,500.00	
Endowment Fund	283,731.86	296,045.25	$12,313.39
General Fund	176,436.22	197,139.74	20,703.52
	$462,668.08	$495,684.99	$33,016.91

"The annual cash income from these securities amounts to approximately $18,500.00 per annum, and the average yield is 3.83 per cent.

"This year the Committee on Finance asked the representative who handles our account at Drexel & Co. to meet with the Committee, in order that we could discuss more in detail certain principles affecting the College investments. Of that you will hear further from the Chairman of the Committee on Finance.

"The services of Drexel & Co. appear to your Treasurer to be entirely satisfactory."

Mr. E. R. Loveland supplemented the Treasurer's Report by saying that the College had just received from Dr. A. B. Brower the second installment of $2,500.00 on the "A. Blaine Brower Traveling Fellowship Fund."

The report of the Treasurer was by resolution accepted.

A resolution was adopted authorizing the House Committee to select chairs and other furniture for the new Second Floor Meeting Room.

Dr. A. B. Brower, Chairman, reported for the Committee on Finance, saying that representatives of our investment counselor's firm had reviewed all of the College investments and discussed same with the Committee. He reported in detail security transactions, both purchases and sales, and received the official approval of the Board of Regents on all transactions affecting the Endowment Fund, in accordance with regulations of the Board.

He stated that the Committee on Finance had further considered the matter of paying travel expenses of the Board of Governors to the Annual Sessions. It had been determined that the cost of train fare alone would amount to approximately eight thousand dollars per annum, and the Committee asked the approval of the Board of Regents to defer the matter for further study for one more year.

On the recommendation of the Committee on Finance, approved by the Board of Regents, the retirement annuity of the Executive Secretary was increased from $200.00 to $500.00 per month.

The Committee on Finance distributed detailed operating statements for the year 1948, including estimates of income and expenses for the balance of the year; compared appropriations and expenditures; reported them in wholly satisfactory condition and recommended their approval, which, by resolution of the Board, was granted.

Dr. Brower then presented the proposed budgets for 1949, calling for an estimated income of $217,030.00 and an estimated expenditure of $206,045.77, and, by resolution, the budgets were adopted.

At this point the publication of a completely revised Directory of the College was reintroduced, and a resolution was adopted approving of the project, subject to the receipt of two thousand pre-publication orders at $4.00 per copy.

The earlier resolution concerning the contribution by the College of $2,000.00 per annum for five years to the World Medical Association was reopened for discussion. It was opposed by some who thought it foreign to the purpose of the College, or inappropriate for other reasons. It was supported by Dr. Ernest E. Irons and Dr. Cyrus C. Sturgis, because the World Medical Association is making a survey of the standards of medical practice, medical education, training of specialists and postgraduate education, and in other ways is engaged in the study of medical scientific problems on an international plane. A resolution was finally adopted deferring the whole matter until the next Annual Session, not to turn it down definitely, but to maintain a sympathetic attitude with the expressed objectives.

Dr. Walter L. Palmer, Chairman of the Board of Governors, reminded the Board that at the San Francisco Annual Session two recommendations from the Credentials Committee—one to make certification a prerequisite for Associateship, and the other to eliminate from future College membership those engaged in the practice of the so-called allied specialties—were held in abeyance. The Minutes of the meeting were

distributed to the Board of Governors by the Executive Secretary and also published in the "ANNALS." Dr. Palmer pointed out that the personnel of the Board of Governors changes fairly rapidly, one-third of them being elected every year, or possibly in some instances at longer intervals. Dr. Palmer stated that the Board of Governors had recommended that a special committee be appointed by the President to study the matter further and before action shall be taken, the Board of Governors be allowed to hear the report and to participate in the discussion of the problem.

Dr. George Morris Piersol pointed out that the proposals were to be reviewed by the Committee on Credentials and the Executive Committee of the Board of Regents before the next Annual Session, and the Governors presumably would be present when the report is brought in for discussion.

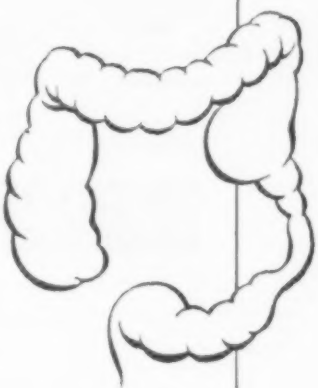
President Walter W. Palmer announced that the Committee on Credentials would meet on February 26, 1949, at the College Headquarters, and on March 26, 1949, at New York, and that the next meeting of the Board of Regents would be held in conjunction with the Board of Governors at the Waldorf-Astoria Hotel, New York City, on March 27, 1949.

Adjournment.

Attest: E. R. LOVELAND,
Secretary

Bowel Management of the Irritable Colon . . .

"As an aid in reestablishing a normal rhythm, the temporary use of a bland bulk-producer . . . may be beneficial. . . . Patients having irritable colon who believe they are suffering from constipation commonly use high-residue diets, . . . They may not realize that this practice is similar to using irritating cathartics or large enemas and often increases the tendency to constipation by increasing spasm of the colon."*



Metamucil is "a bland bulk-producer" which gently initiates reflex peristalsis and movement of the intestinal contents. The "smoothage" therapy of Metamucil encourages a return of the normal function of the colon without irritating the mucosa.

METAMUCIL®

is the highly refined mucilloid of Plantago ovata (50%), a seed of the psyllium group, combined with dextrose (50%) as a dispersing agent.

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY

SEARLE RESEARCH IN THE SERVICE OF MEDICINE

*Collins, E. N.: The Diagnosis and Treatment of Irritable Colon: Physiologic, Local, Irritative and Psychosomatic Factors, M. Clin. North America 32:398 (March) 1948.

AT HOME OR AWAY SPOT TESTS SIMPLIFY URINALYSIS

No Test Tubes • No Measuring • No Boiling

Diabetics welcome "Spot Tests", (ready to use dry reagents), because of the ease and simplicity in using. No test tubes, no boiling, no measuring; just a little powder, a little urine—color reaction occurs at once if sugar or acetone is present.

Galatest . . . Acetone Test (DENCO)

FOR DETECTION OF SUGAR IN THE URINE — FOR DETECTION OF ACETONE IN THE URINE

SAME SIMPLE TECHNIQUE FOR BOTH

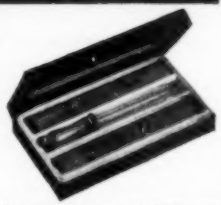
1. A LITTLE POWDER

2. A LITTLE URINE

COLOR REACTION IMMEDIATELY

Accepted for advertising in the Journal of the A.M.A.

WRITE FOR DESCRIPTIVE LITERATURE



A carrying case containing one vial of Acetone Test (Denco), one vial of Galatest, medicine dropper and Galatest color chart is now available at all prescription pharmacies and surgical supply houses. This is very convenient for the medical bag or for the diabetic patient.

Acetone Test (DENCO) *Galatest*

THE DENVER CHEMICAL MANUFACTURING COMPANY, INC.
163 Varick St., New York 13, N. Y.

for Fifty Years

PROFESSIONAL PROTECTION EXCLUSIVELY

THE MEDICAL PROTECTIVE COMPANY
FORT WAYNE, INDIANA

Patricia Edgerly

SPECIALIZING IN MEDICAL PLACEMENTS SINCE 1926!

BOOTH 54, TECHNICAL EXHIBIT, 30TH ANNUAL SESSION, MARCH 28–APRIL 1

Do you need a well trained and competent associate or assistant, hospital administrator, laboratorian, or other medical assistant?

Do you want a good appointment in one of the above capacities?

Our successful experience in serving the medical field exclusively since 1926 is the best assurance that we can be of use to you. During these years we have placed many internists, pathologists, radiologists, neurologists, et al., with outstanding physicians, groups, industrial firms and institutions. We constantly strive to arrange the placement which is of mutual benefit and hence lasting. Our experience will be valuable to you, as it has been to many, whether your problem be to find the best man or the best opening. Talk with us at *Booth 54*, or write to—

THE NEW YORK MEDICAL EXCHANGE

The largest and oldest medical personnel bureau in the east

489 FIFTH AVENUE **NEW YORK**

Suite 605 **Murray Hill 2-0676**

The I.E.C. *Simplified*

NEGATIVE PRESSURE SINUS UNIT

. . . provides suction during the negative pressure cycle for effective application of penicillin aerosol inhalation in the treatment of acute and chronic sinusitis.

During the inhalation phase the patient takes four respirations, breathing in and out of the mouth, allowing the nasal cavities to be filled with penicillin aerosol.

The suction phase commences as the patient removes her finger from the end of the venturi tube and swallows. This action creates a suction which evacuates air and secretions from the nasal accessory sinuses and permits penicillin aerosol to be drawn into these cavities. *These phases are alternately repeated until the prescribed dosage is used.*

Ref.: A. L. Barach, M.D., M. Soroka, B.S., et Al. *New York State J. Med.*, vol. 47, No. 13 (July 1947).

WRITE PROFESSIONAL SERVICE DEPARTMENT FOR LITERATURE

Inhalational Equipment Company Inc.

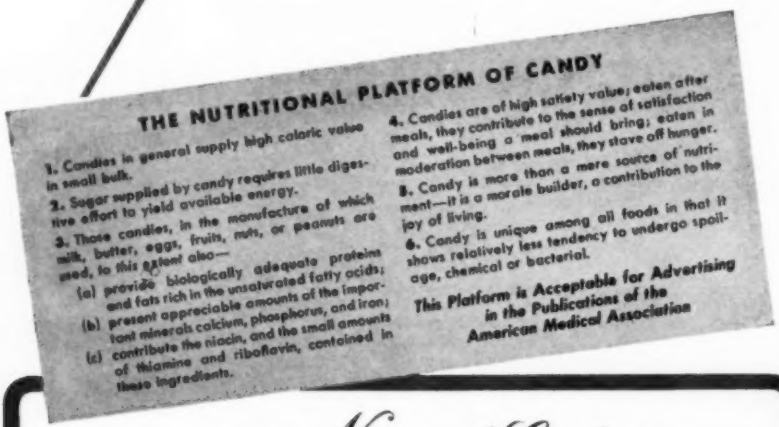
248 EAST 119th STREET • NEW YORK 35, N.Y.

THE PLACE OF *Candy* IN THE *Balanced Diet*

In a carefully chosen, well balanced dietary providing all essential nutrients in proper amounts, there is adequate provision for foods which do more than merely satisfy nutrient needs—foods which are especially tempting to the palate. Candy is that kind of food.

Supplying valuable caloric food energy, it also imparts to a meal a finishing touch of which few other foods are capable. Candy, with its almost irresistible attraction, need not be denied children or adults providing the dietary is adequate in all other respects. In fact, candy at the conclusion of a meal imparts a feeling of satiety and a sense of having eaten well, both of which enhance the functioning of the digestive processes.

Many candies are made of valuable foods in addition to sugar—butter, milk, cream, eggs, nuts and peanuts—and to the extent these foods are present, candies contribute biologically adequate protein, vitamins, and minerals.


THE NUTRITIONAL PLATFORM OF CANDY
1. Candies in general supply high caloric value in small bulk.
2. Sugar supplied by candy requires little digestive effort to yield available energy.
3. Those candies, in the manufacture of which milk, butter, eggs, fruits, nuts, or peanuts are used, to this extent also—
(a) provide biologically adequate proteins and fats rich in the unsaturated fatty acids;
(b) present appreciable amounts of the important minerals calcium, phosphorus, and iron;
(c) contribute the niacin, and the small amounts of thiamine and riboflavin, contained in these ingredients.
4. Candies are of high satiety value; eaten after meals, they contribute to the sense of satisfaction and well-being a meal should bring; eaten in moderation between meals, they stave off hunger.
5. Candy is more than a mere source of nutriment—it is a morale builder, a contribution to the joy of living.
6. Candy is unique among all foods in that it shows relatively less tendency to undergo spoilage, chemical or bacterial.
This Platform is Acceptable for Advertising in the Publications of the American Medical Association

COUNCIL ON CANDY OF THE *National Confectioners'* *Association*

1 NORTH LA SALLE STREET CHICAGO 2, ILLINOIS

Exhibit of the

GRADWOHL LABORATORIES, St. Louis, Missouri

Members of the College are invited to visit our **Booth No. 85** at the coming meeting at the Waldorf-Astoria Hotel. Dr. Gradwohl will be there in person to discuss any problem which you may wish to take up with him, relative to the laboratory activities; namely, laboratory reagents, training of technicians, new literature on laboratory procedures, etc. Special attention is called to our interest in the cytological diagnosis of cancer.

We hope to have the privilege of meeting you in New York.

GRADWOHL LABORATORIES

3514 Lucas Ave. **St. Louis 3, Missouri**

R. B. H. Gradwohl, M.D., Director

What you'd look for In an Internist

Visit us during the College Meeting, March 28–April 1. Our booth is 107.

Undoubtedly, your first requisite would be well rounded training and experience governed by an alert, scientific mind and sound judgment.

Our internist meets this requirement and more. He's in his middle thirties, a Board man with teaching as well as good clinical experience to his credit.

You would want him as an associate in your private practice, or in your group. If possible, he would like to continue part-time teaching.

Wire or write us if interested. All negotiations confidential.

This man of whom we write is one of our great group of well trained internists qualified to meet your requirements.

BURNEICE LARSON, *Director*
THE MEDICAL BUREAU
Palmolive Bldg., at 919 N. Michigan Ave.
CHICAGO - - - ILLINOIS

A Pleasant Way to Prescribe Choline...

syrup CHOLINE (FLINT)

Representing Choline Dihydrogen Citrate 25% W/V

Only within the present decade has choline assumed its important position as a vital part of the dietary treatment of hepatic dysfunction.

Palatable Syrup Choline Dihydrogen Citrate (Flint) may be used as a supplement to other therapeutic measures in the treatment of chronic liver involvement in diabetes, in malnutrition, in poisoning by hepatoxic agents, in various infectious processes and in cirrhosis.

"Syrup Choline (Flint)," containing 1 gram Choline Dihydrogen Citrate in each 4 cc., is supplied in pint and gallon bottles.

CHOLINE will be featured at Booths 18 and 19 at the 1949 convention of the AMERICAN COLLEGE OF PHYSICIANS.

For your copy of "The Present Status of Choline Therapy in Liver Dysfunction," write:

FLINT, EATON & COMPANY
DECATUR, ILLINOIS

Gelatine's effective hematopoietic action in NUTRITIONAL ANEMIA

Hemoglobin is a conjugated protein and depends upon a liberal dietary source of protein for its production in the treatment of anemia.

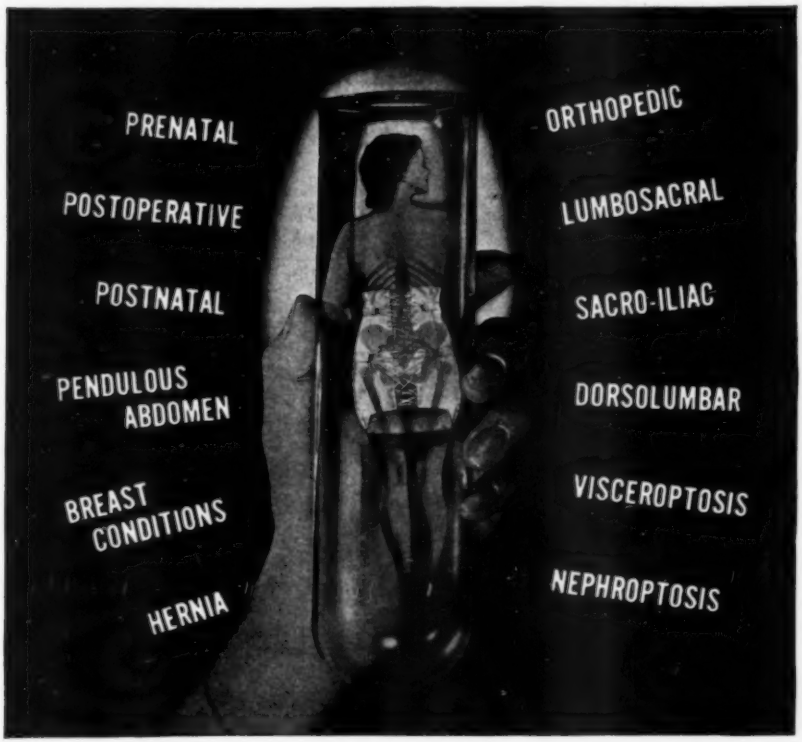
Knox Gelatine U.S.P., which is made exclusively of selected bone stock, has a good proportion of the amino acids found to be of hematopoietic value. One ounce of Knox unflavored gelatine daily in divided doses with meals, taken in water, fruit juice or milk and in conjunction with suitable iron medication, has been found of value in nutritional anemia.

Knox unflavored Gelatine U.S.P., unlike the ready-flavored gelatine powders, is *all* protein, no sugar. So it is well to specify Knox by name.

KNOX

Gelatine U.S.P.

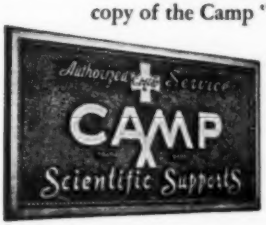
ALL PROTEIN · NO SUGAR · NO FLAVORING



Consistent Research Makes Scientific Design Basic In

CAMP SCIENTIFIC SUPPORTS

For many decades it has been our privilege to work closely with physicians and surgeons in the design, improvement and manufacture of anatomical supports to meet the needs of their patients. The unique Camp adjustment feature insures proper firmness about the pelvis and controlled support of the abdomen, spinal column and gluteal region without compression. Write for your copy of the Camp "Reference Book for Physicians and Surgeons."



THIS EMBLEM is displayed only by reliable merchants in your community. Camp Scientific Supports are never sold by door-to-door canvassers. Prices are based on intrinsic value. Regular technical and ethical training of CAMP fitters insures precise and conscientious attention to your recommendations.

S. H. CAMP and COMPANY, Jackson, Michigan
World's Largest Manufacturers of Scientific Supports
Offices in New York • Chicago • Windsor, Ontario • London, England

May We Help You

At the New York Session?

We are looking forward with cordial interest to our participation in the Annual Session at New York, and to the pleasure of contacts with friends—old and new. You are particularly invited to consult us in Booth 17 . . .

IF you are seeking a properly qualified candidate for a post in hospital, clinic or your own office—OR

IF you will be available during the coming months for one of the better opportunities now being listed with us.

You'll find us prepared to refer to our files for information on select candidates now available in many fields, also to supply on-the-spot data on some especially attractive current openings.

You will also find us equipped by our more than fifty years of service *to follow through with well-advised assistance* in solving your personnel and placement problem—whatever its nature.

Let's discuss it at the Annual Session—Booth 17.

Ann Woodward, Director

Woodward

MEDICAL PERSONNEL BUREAU

Ninth Floor, 185 N. Wabash Ave.

CHICAGO 1, ILLINOIS

Our Fifty-third Year

LaMOTTE BLOOD CHEMISTRY OUTFITS

A complete line of approved Blood Chemistry Outfits, simplified so as to render accurate results with minimum time and operation.

Units available for

Albumin and Sugar in Urine	pH of Blood
Alcohol in Blood and Urine	pH of Urine
Alveolar Air CO_2 Tension	Phenolsulfonphthalein (Block Type)
Bilirubin in Blood	Phenolsulfonphthalein (Roulette Type)
Blood Loss in Body Fluids	Specific Gravity (Blood and Body Fluids)
Bromides in Blood	Sugar in Blood
Calcium-Phosphorus in Blood	Sugar in Urine
Chlorides in Blood	Sulfonamides (Blood and Urine)
Cholesterol in Blood	Thiocyanate
Creatinine in Blood	Thymol Turbidity Test
Gastric Acidity	Urea in Blood
Hemoglobinometer	Urea in Urine
Icterus Index (Pigford)	Uric Acid in Blood
Icterus Index (Micro)	Urinalysis
Kline Test for Syphilis	Vitamin C in Blood and Urine

Information on above cheerfully furnished.

If you do not have The LaMotte Blood Chemistry Handbook, a complimentary copy will be sent upon request.

LaMotte Chemical Products Co.

Dept. "C" Towson, Baltimore 4, Md.

WANTED

Copies of

ANNALS OF INTERNAL MEDICINE

Good used copies of the *following* issues are now needed. Only those issues which are currently being advertised can be accepted.

$1.25 each for

Vol. II, No. 5—November, 1928
Vol. XXV, No. 1—July, 1946

75¢ each for

Vol. XXVIII, No. 1—January, 1948
Vol. XXIX, No. 1—July, 1948
Vol. XXIX, No. 3—September, 1948

Address journals to:

E. R. LOVELAND, Executive Secretary

4200 Pine Street Philadelphia 4, Pa.

POSTGRADUATE COURSES

Offered by the

AMERICAN COLLEGE OF PHYSICIANS

January through June, 1949

No. 1—MEDICAL ASPECTS OF NUCLEAR ENERGY; U. S. Army Medical Center, Washington, D. C.; January 24–February 1; Armed Forces Special Weapons Project and the American College of Physicians; Lt. Col. Karl Houghton, (MC), USA, *Director*. This course has been concluded.

No. 2—GASTRO-ENTEROLOGY; The Stanford University School of Medicine and The University of California Medical School, San Francisco, Calif.; February 7–12; Dwight L. Wilbur, M.D., F.A.C.P., and T. L. Althausen, M.D., F.A.C.P., *Directors*. This course has been concluded.

No. 3—CLINICAL MEDICINE FROM THE HEMATOLOGIC VIEWPOINT; Ohio State University College of Medicine, Columbus, Ohio; February 14–19; Charles A. Doan, M.D., F.A.C.P., *Director*. This course has been concluded.

No. 4—INTERNAL MEDICINE; Massachusetts General Hospital, Boston, Mass.; 2 weeks, March 7–19: $60.00, A. C. P. Members; $120.00, Non-members. Exercises in application of theory to practice. General topics: endocrinology, cancer, cardiovascular diseases, nutritional problems of gastro-intestinal diseases, preventive aspects of clinical medicine, rheumatoid arthritis. James H. Means, M.D., F.A.C.P., *Director*.

No. 5—ELECTROCARDIOGRAPHY; Massachusetts General Hospital, Boston, Mass.; 1 week, April 25–30; $60.00, A. C. P. Members; $120.00, Non-members. Basic principles of electrocardiography; interpretation based on current knowledge of the physiology of heart muscle. Conger Williams, M.D., *Director*. This course has been registered to full capacity.

No. 6—DISEASES DUE TO ALLERGIC AND IMMUNE MECHANISMS; Haddon Hall Hotel, Atlantic City, N. J.; 4 days, April 28–May 1; $30.00, A. C. P. Members; $60.00, Non-members. Immunology, pharmacology, physiology, and clinical phases of diseases caused by immune mechanisms. Given at Atlantic City for convenience of physicians having meetings there at the time. Leo H. Criep, M.D., Associate Professor of Medicine, University of Pittsburgh, *Director*.

No. 7—CARDIOVASCULAR DISEASE; Philadelphia Institutions; 1 week, May 2–7; $30.00, A. C. P. Members; $60.00, Non-members. Lectures, panel discussions and clinical demonstrations; recent advances in knowledge, diagnosis and treatment. William G. Lennan, Jr., M.D., F.A.C.P., Professor of Medicine, Woman's Medical College of Pennsylvania, *Director*.

No. 8—PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE; University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa.; 1 week, May 9–14; $30.00, A. C. P. Members; $60.00, Non-members. Why symptoms occur; how drugs act; why and how clinical physiological tests are used in diagnosis. Julius H. Comroe, Jr., M.D., F.A.C.P., *Director*.

No. 9—ENDOCRINOLOGY; Tufts College Medical School, Boston, Mass.; 1 week, June 13–18; $30.00, A. C. P. Members; $60.00, Non-members. Emphasis on fundamental sciences contributing to endocrinology and recent advances in clinical endocrinology. Edwin B. Astwood, M.D., F.A.C.P., *Director;* E. W. Dempsey, Ph.D., and Roy O. Greep, Ph.D., *Associate Directors*.

FOR DETAILED INFORMATION AND REGISTRATION BLANKS, address The Executive Secretary, American College of Physicians, 4200 Pine St., Philadelphia 4, Pa.

ANNALS OF INTERNAL MEDICINE

Official Periodical of the American College of Physicians

Place of Publication—Prince and Lemon Sts., Lancaster, Pa.

Editorial Office—University Hospital, Baltimore 1, Md.

Executive Office—4200 Pine Street, Philadelphia 4, Pa.

The Annals of Internal Medicine is published by the American College of Physicians. The contents consist of contributions in the field of internal medicine, editorials, book reviews, and a section devoted to the affairs of the College.

Manuscripts. All correspondence relating to the publication of papers and all books and monographs for review should be addressed to the Editor. No manuscripts will be accepted without his consideration. Bibliographic references are to conform to the following style:

4. Doe, J. E.: What I know about it, Jr. Am. Med. Assoc., 1931, xcvi, 2006–2008.

Six illustrations per article are allowed without cost to the author. Beyond this number the author must pay the actual cost of illustrations.

Reprints. For each article published, there will be furnished gratis fifty reprints without covers. An order slip for additional reprints, with a table showing cost, will be sent with galley proof to each contributor. If additional reprints over the first fifty are wanted the order slip must be returned to the printer at the time corrected galley proofs are sent to the Editor.

Reviews. The Annals will make an especial feature of the reviews of monographs and books bearing upon the field of internal medicine. Authors and publishers wishing to submit such material should send it to the Editor. While obviously impossible to make extended reviews of all material, an acknowledgment of all books and monographs sent will be made in the department of reviews.

Subscription. This periodical is issued monthly, new volumes beginning with the January and July numbers of each year. Subscriptions may be by volume or by year. Volumes will consist of approximately 1,300 pages. Subscription price per annum, net postpaid: $10.00, United States, Canada, Mexico, Cuba, Hawaii, Puerto Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries. Prices for back volumes or numbers furnished upon application. Single numbers, current volume, when available, $1.25. Members of the American College of Physicians receive the Annals of Internal Medicine in connection with the payment of annual membership dues, of which nine dollars is for a year's subscription to the publication. Checks should be drawn to the order of W. D. Stroud, M.D., Treasurer, and remitted through the Publication Office or the Executive Secretary's Office.

Business Correspondence. All correspondence relating to business matters, advertising, subscriptions to the Annals, inquiries concerning membership in the American College of Physicians, et cetera, should be addressed to the Publication Office or to the Executive Secretary. Books and reprints presented to the College Library should be addressed to the Executive Secretary.

Associate Editors

David P. Barr ..... New York
Robert A. Cooke ..... New York
James H. Means ..... Boston
O. H. Perry Pepper ..... Philadelphia
James J. Waring ..... Denver

Assistant Editor

Paul W. Clough ..... Baltimore

EDITOR

Maurice C. Pincoffs, M.D.
University Hospital
Baltimore 1, Md.

EXECUTIVE SECRETARY

Edward R. Loveland
American College of Physicians
4200 Pine Street, Philadelphia 4, Pa.

Lancaster Press, Inc., Lancaster, Pa.